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ESTRÉS OXIDATIVO Y SUPLEMENTACIÓN DE ÁCIDO FERÚLICO EN OVINOS DE PELO ENGORDADOS EN UN AMBIENTE DE ESTRÉS POR CALOR

TESIS

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La presente tesis titulada "**Estrés oxidativo y suplementación de ácido ferúlico en ovinos de pelo engordados en un ambiente de estrés por calor**" realizada por la **C. Karen Mariela Valadez García**, y dirigida por el **Dr. Ulises Macías Cruz**, ha sido evaluada y aprobada por el Comité Particular abajo indicado, como requisito parcial para obtener el grado de:

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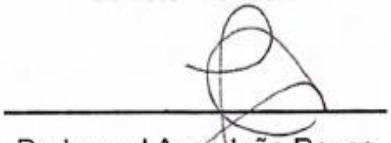

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Resumen

Las altas temperaturas ambientales (Ta) que prevalecen durante el verano en regiones áridas y semiáridas promueven estrés térmico-oxidativo en los ovinos de pelo y, consecuentemente, afectaciones negativas en su producción de carne. Por lo tanto, se realizaron dos estudios en verano para generar conocimiento en relación con los mecanismos biológicos de la presencia de estrés oxidativo, así como el uso de ácido ferúlico (AF) como estrategia de mitigación del estrés por calor (EC) en la engorda de ovinos de pelo. El estudio 1 se realizó con 22 corderas Dorper x Katahdin que fueron alojadas en corraletas individuales durante 40 días para determinar los principales factores ambientales, fisiológicos, metabólicos y de comportamiento productivo asociados con la presencia de estrés oxidativo. Los factores se definieron aplicando las siguientes pruebas estadísticas: análisis de correlación de Pearson, componentes principales y análisis de regresión lineal múltiple. Se observó que una frecuencia respiratoria baja en la mañana (R^2= 0.46) y un aumento en las concentraciones de insulina (R^2= 0.06) promueven un aumento ($P \leq 0.01$) en la oxidación de proteínas. La disminución en las Ta máximas favoreció el aumento ($P < 0.01$) en la oxidación de lípidos (malondialdehído; R^2= 0.43) y capacidad oxidante total (R^2= 0.73). El aumento en el índice de temperatura-humedad máximo (R^2= 0.52) causó una reducción ($P < 0.01$) en la capacidad antioxidante total. En general, el índice de estrés oxidativo aumentó ($P \leq 0.04$) a medida que también incrementó la humedad relativa máxima (R^2= 0.13) y la ganancia diaria de peso (GDP; R^2= 0.04). El estudio 2 también se realizó con 22 corderas Dorper x Katahdin alojadas en corraletas individuales, las cuales se dividieron en dos grupos (testigo vs. suplementación con AF por 40 días) bajo un diseño de bloques completamente al azar para evaluar el efecto del AF sobre el estado oxidativo, comportamiento productivo, características de la canal, rendimiento de cortes primarios y calidad de la carne. La suplementación de AF tendió ($P= 0.06$) a disminuir la oxidación de proteína, sin afectar la oxidación de grasas o el índice de estrés oxidativo. Similarmente, el AF aumentó la GDP y la eficiencia alimenticia solamente en los días más cálidos; asimismo, modificó ($P \leq 0.05$) la deposición de grasa y músculo en canal, sin afectar ($P \geq 0.11$) el peso y rendimiento de la canal, así como la calidad de

la carne. En conclusión, las condiciones climáticas y la frecuencia respiratoria son los principales factores asociados con la presencia de estrés oxidativo en las corderas de pelo estresadas por calor. Además, el AF reduce la oxidación de proteína beneficiando el crecimiento de las corderas solamente en condiciones de EC extremo.

Palabras clave: ovinos de pelo, climas cálidos, estrés oxidativo, antioxidantes naturales, compuestos fenólicos.

Abstract

The high ambient temperatures (Ta) that prevail during the summer in arid and semi-arid regions promote thermal-oxidative stress in hair sheep and, consequently, negative effects on their meat production. So, two studies were carried out during the summer season to generate knowledge about the biological mechanisms involved in presence of oxidative stress, as well as the use of ferulic acid (FA) as a mitigation strategy for heat stress (HS) in fattening hair sheep. Experiment 1 was carried out with 22 Dorper x Katahdin ewe lambs housed in individual pens for 40 days to determine the main environmental, physiological, metabolic, and performance factors associated with the oxidative stress. The factors were defined by applying the following statistical analysis: Pearson's correlation, principal components and multiple linear regression. A low respiratory rate in the morning (R^2= 0.46) and an increase in insulin concentrations (R^2= 0.06) promoted an increase ($P \leq 0.01$) in protein oxidation. The decrease in maximum Ta promoted the increase ($P < 0.01$) in lipid oxidation (malondialdehyde; R2= 0.43) and total oxidant capacity (R^2= 0.73). The increase in the maximum temperature-humidity index (R^2= 0.52) caused a reduction ($P < 0.01$) in the total antioxidant capacity. In general, the oxidative stress index increased ($P \leq 0.04$) as the maximum relative humidity (R^2= 0.13) and the average daily gain (ADG; R^2= 0.04) also increased. Experiment 2 was also conducted with 22 Dorper x Katahdin ewe lambs housed in individual pens, which were divided into two groups (control *vs.* FA supplementation for 40 days) under a completely randomized block design to assess the effect of FA on the oxidative status, feedlot performance, carcass characteristics, wholesale cut yields, and meat quality. The FA supplementation tended (P= 0.06) to decrease protein oxidation without affecting fat oxidation or overall oxidative stress index. Similarly, FA increased ADG and feed efficiency only on hottest days; likewise, it modified ($P \leq 0.05$) fat and muscle deposition in carcass without affecting ($P \geq 0.11$) carcass weight and yield and the meat quality. In conclusion, climatic conditions and respiratory rate are the main factors associated with presence of oxidative stress in heat-stressed hair lambs. In addition, FA supplementation reduces protein oxidation benefiting ewe lambs' growth, but only under extreme HS conditions.

Keywords: Hair sheep, hot climates, oxidative stress, natural antioxidants, phenolic compounds.

CAPÍTULO I. INTRODUCCIÓN

Alrededor del 60% de la población ovina mundial (1´263,136,644 cabezas) se localiza en regiones áridas y semiáridas (FAOSTAT, 2021), las cuales se caracterizan por la prevalencia de condiciones climáticas extremas, escasa precipitación pluvial y baja disponibilidad de alimento (Sejian et al., 2017). Las condiciones climáticas más severas se presentan durante el verano, época en la que las altas temperaturas ambientales (Ta) generan en los ovino estrés por calor (EC) al exceder su temperatura confort (12 a 30 °C; Vicente-Pérez et al., 2020). El EC es un problema global que disminuye la producción de carne ovina en las regiones cálidas, asociado principalmente con un aumento en los requerimientos nutricionales de mantenimiento, disminución del consumo de alimento y alteraciones en el metabolismo (Marai et al., 2007; Macías-Cruz et al., 2020; Nicolás-López et al., 2021a). Aunado a lo anterior, el EC promueve estrés oxidativo en los ovinos, alterando de este modo la integridad estructural y funcional de sus órganos y tejidos y, por consiguiente, su crecimiento (Belhadj et al., 2019; Nicolás-López et al., 2021b). De este modo, los corderos estresados por calor disminuyen su ganancia diaria de peso (GDP) y eficiencia alimenticia, y presentan detrimentos en sus atributos de la canal y calidad de la carne (Macías-Cruz et al., 2020; Zhang et al., 2021).

Actualmente se implementan diferentes estrategias de manejo, adaptación de instalaciones y modificaciones nutricionales para mitigar los efectos del EC en la producción de carne ovina (Sejian et al., 2017). No obstante, dadas las tendencias actuales por producir de forma “limpia, verde y ética”, la investigación en los últimos años se ha enfocado en demostrar que el uso de compuestos naturales con propiedades antioxidantes podría ser una alternativa viable para mejorar la producción de carne ovina en climas cálidos. Así, en corderos de lana estresados por calor se ha demostrado que la suplementación de algunos compuestos flavonoides (Alhidary & Abdelrahman, 2016), carotenoides (Jiang et al., 2015) y fenoles (Liu et al., 2016) mejoran el comportamiento productivo, incrementan el rendimiento de la canal caliente y retardan la peroxidación lipídica en el músculo esquelético. Sin embargo, la información sobre el uso de antioxidantes naturales en la producción de carne ovina bajo escenarios estresantes continúa siendo incipiente.

El ácido ferúlico (AF; ácido (E)-3-(4-hidroxi-3-metoxi-fenil) propil -2-ecoico) es un fitoquímico derivado principalmente de cereales, el cual tiene múltiples propiedades benéficas para la salud, bienestar y producción animal (de Oliveira & Batista, 2017). El AF, además de ser un potente antioxidante, también actúa como antiinflamatorio, y modulador del metabolismo, de la respuesta al choque térmico y la hipertrofia muscular (Kumar & Pruthi, 2014; Chodkowska et al., 2018; He et al., 2018; Peña-Torres et al., 2020). Algunos estudios en corderos evidenciaron que el AF no mejora el crecimiento y la deposición de masa muscular en un ambiente termoneutral (TN; Macías-Cruz et al., 2014), pero sí en condiciones de estrés por frío como resultado de una mejor defensa antioxidante en los animales que lo consumieron (Wang et al., 2019a). Similarmente, en cerdos (Valenzuela-Grijalva et al., 2021; Wang et al., 2021) y bovinos (Peña-Torres et al., 2020) de engorda este fenol ha demostrado su capacidad como promotor de crecimiento. Por lo cual, el uso de este compuesto fenólico podría ser más efectivo que otros compuestos antioxidantes para reducir los efectos negativos de las altas temperaturas en ovinos de engorda, aunque esto aún requiere ser demostrado.

Los efectos detrimentales del EC en la producción de carne ovina varían entre razas. Los ovinos de pelo, en comparación con las razas de lana y otras especies domésticas, son animales termorresistentes que han demostrado capacidad de continuar creciendo y reproduciéndose bajo las condiciones bioclimáticas extremas de zonas áridas y semiáridas (Vicente-Pérez et al., 2020). Esto atribuido a que cuentan con mecanismos adaptativos fenotípicos, fisiológicos, metabólicos y celulares para tolerar con mayor eficiencia las temperaturas altas (Macías-Cruz et al., 2016, 2018, 2020; Nicolás-López et al., 2021). Si bien, los ovinos de pelo siguen creciendo bajo EC, su ganancia de peso y eficiencia alimenticia disminuye en alrededor de 25 % sin afectar el consumo de alimento (Macías-Cruz et al., 2020). Por consiguiente, al igual que en razas de lana, la búsqueda de estrategia para mitigar los efectos del EC es una necesidad. La adición de AF a la dieta de finalización de la engorda podría ser una alternativa, dado sus beneficios como antioxidante y demás propiedades. Aunque, antes es necesario dilucidar los mecanismos biológicos asociados al daño oxidativo en corderos de pelo estresados por calor.

1.1. Hipótesis

1) Los factores climáticos, fisiológicos, metabólicos y de comportamiento productivo contribuyen a incrementar las concentraciones séricas de biomarcadores de estrés oxidativo en corderas de pelo bajo EC ambiental.

2) La suplementación de AF mejora el crecimiento, características de canal y calidad de la carne al reducir el estrés oxidativo en corderas de pelo estresadas por calor.

1.2. Objetivos

1) Establecer la relación entre biomarcadores séricos de estrés oxidativo con variables climáticas, respuesta fisiológica, metabolismo y comportamiento productivo de corderas de pelo expuestas a EC ambiental.

2) Evaluar el efecto del AF sobre marcadores del estado oxidativo, comportamiento productivo, características de canal, rendimiento de cortes primarios y calidad de carne en corderas de pelo estresadas por calor.

CAPÍTULO II. REVISIÓN DE LITERATURA

2.1. Ovinos de pelo frente a la demanda mundial y nacional de carne

El crecimiento demográfico, la urbanización y el mayor poder adquisitivo en los países en desarrollo han incrementado la demanda mundial de carne (FAO, 2021a). De acuerdo con proyecciones de la Organización para la Cooperación Económica y el Desarrollo (OCDE-FAO, 2021), en el 2029 la producción mundial de carne aumentará 40 millones de toneladas con respecto a la producción del 2017-2019, alcanzando una producción total de 366 millones de toneladas. Para abastecer las cifras anteriores, más de dos terceras partes de la producción adicional serán cubiertas por la carne de pollo (51%) y de cerdo (28%), mientras que la carne de bovinos y ovinos solo aportarán el 15 y 6%, respectivamente. En específico, se prevé que en el 2029 la demanda mundial de carne ovina incrementará 20% con respecto a los 9.9 millones de toneladas producidas actualmente. La mayor parte de dicho incremento será abastecido por China, Australia y Nueva Zelanda -principales productores actuales de carne ovina- y, adicionalmente, por países económicamente vulnerables de Asia y de África (FAOSTAT, 2021).

A pesar de que la carne ovina, junto con la de caprino, son la que menos aporte tienen en la producción mundial de carne, estas continuarán siendo las principales fuentes de proteína animal en entornos marginales. Según las últimas cifras oficiales (FAOSTAT, 2021), el inventario mundial de ovinos es de más de 1**,**260 millones de cabezas, las cuales se concentran principalmente en países de Asia (43%) y África (33%) caracterizados por un bajo desarrollo y una alta prevalencia de subalimentación (FAO, 2019a; Programa Mundial de Alimentos, 2021). Si bien esta distribución limita el desarrollo de la ovinocultura mundial por la falta de insumos y tecnología, para los países con déficit de alimentos, los ovinos seguirán siendo una alternativa para combatir el hambre y generar ingresos (Binsiya et al., 2017). Es por ello que, desde la década de los 50s hasta la fecha, investigadores y productores se han enfocado en la selección de razas nativas de lana y de pelo, así como de genotipos criollos, las cuales debido a su capacidad de adaptación a diferentes

zonas agroecológicas y sistemas de producción (FAO, 1991; Sejian et al., 2018), garantizan la producción de carne (FAO, 2019a).

Con respecto al panorama nacional mexicano, la producción de carne de ovino es baja en comparación con la carne de otras especies; sin embargo, en los últimos años ha incrementado para satisfacer la demanda nacional. De acuerdo con el Servicio de Información Agroalimentaria y Pesquera (SIAP, 2021), en 2020 se registró una producción nacional de carne de 7,438,206 t. Las especies que más contribuyeron a dicha cifra fueron las aves (48%), los bovinos (28%) y los cerdos (22%), mientras que los ovinos solo cubrieron 0.88% y los caprinos 0.54 % de la producción total. Durante el mismo año, la producción nacional de carne de ovino alcanzó las 64,758 t, siendo esta cifra la más alta reportada hasta el momento en el país (SIAP, 2021). Las entidades con mayor aporte a la producción nacional fueron el Estado de México (14%), Hidalgo (10%) y Veracruz (9%). En términos de demanda de carne ovina, con respecto al 2019, durante el 2020 la pandemia de COVID-19 ocasionó un ligero descenso en el consumo nacional interno (-7%) y el consumo per cápita (-17%), reportándose una cifra de 68,282 t y 0.5 kg, respectivamente (Consejo Mexicano de la Carne, 2019, 2021; Marchant-Forde & Boyle, 2020). A pesar de lo anterior, actualmente la producción de carne ovina muestra una clara tendencia a continuar incrementando su volumen y disminuir las importaciones (Arteaga-Castelán, 2014). 8,725,882

Los ovinos de pelo han contribuido a la mayor producción de carne ovina en el país (Arteaga-Castelán, 2007). La primera raza de pelo de la que se tiene registro en México es la Pelibuey, la cual fue introducida entre 1940 y 1950 a través de la península de Yucatán. Debido a su rusticidad y baja estacionalidad reproductiva, el uso de esta raza se popularizó inicialmente en regiones tropicales y, posteriormente, en todo el territorio nacional (Aguilar-Martinez et al., 2017). Sin embargo, dado el bajo rendimiento productivo de los ovinos Pelibuey, en la década de los 90’s se introdujeron las razas de pelo especializados en la producción de carne Katahdin y Dorper (Arteaga-Castelán, 2007; Chay-Canul et al., 2016).

Actualmente, la producción de carne ovina se basa en la engorda y sacrificio de ovinos de las razas Katahdin, Dorper y Pelibuey, así como sus diferentes cruzas (Partida de la Peña et al., 2017). Cabe mencionar que, a pesar de la importancia de las razas de pelo en la producción de carne ovina en el país, no existen datos recientes de la población existe de ellos; no obstante, en 2000, se estimó que su población representaba el 23% de los ovinos existentes en el país (Aguilar-Martinez et al., 2017). Ante el incremento de la población ovina de pelo, aunado a la sustitución de la lana y el algodón por el uso de fibras sintéticas en la industria textil (Elvira-Mario, 2017), la población de ovinos de lana disminuyó en el país. Por lo cual, actualmente el objetivo de la ovinocultura mexicana se ha orientado principalmente hacia la producción de carne, empleando en su mayoría razas puras de ovinos de pelo y sus diferentes esquemas de cruzamiento (Partida de la Peña et al., 2013, 2017). De este modo, el uso de estos genotipos con reducido anestro estacional ha garantizado la producción constante de corderos y, por lo tanto, contribuido a que la producción nacional de carne ovina incrementara en las últimas décadas (Soto & Delgado, 2010).

En el futuro, los ovinos de pelo serán una de las especies más viables para producir carne bajo sistemas de producción sustentable (Caroprese et al., 2015). Ante la creciente demanda mundial y nacional de carne, el sector pecuario debe incrementar su producción cárnica implementando estrategias sustentables, es decir, factibles desde el punto de vista ambiental, económico y social (FAO, 2021b). Bajo este contexto, en comparación con otras especies y ovinos de lana, el uso de ovinos de pelo cobrará importancia en los siguientes años (Di Trana et al., 2015; Sejian et al., 2019). Lo anterior está asociado a la capacidad que poseen dichas razas de producir y reproducirse en ambientes con climas favorables y con alta disponibilidad de recursos naturales, hasta regiones con climas extremos y con escasos recursos vegetales (Vicente-Pérez et al., 2020). Por lo cual, estas razas cobrarán mayor importancia como un recurso genético para aprovechar los recursos naturales de manera eficiente y, al mismo tiempo, contribuir a la rentabilidad de los sistemas de producción y a garantizar la oferta de carne (Partida de la Peña et al., 2013).

2.2. Los ovinos de pelo en la producción de carne en regiones áridas

Actualmente la mayor parte del territorio mundial y nacional presenta condiciones bioclimáticas de tipo áridas, situación que se prevé incremente en los siguientes años. De acuerdo con la actual clasificación climática de Köppen (Beck et al., 2018), cerca de una tercera parte de la superficie terrestre presenta zonas áridas y el resto climas fríos (25%), tropicales (22%), templados (16%) y polares (7%). A nivel nacional, la extensión de las regiones áridas es del 53.11% del territorio mexicano, seguida de regiones tropicales (35.81%), templadas (11%) y frías (0.03%) (SEMARNAT, 2021). Sin embargo, durante el presente siglo se prevé que la proporción de regiones cálidas y secas incrementen debido a una excesiva concentración atmosférica de gases de efecto invernadero (GEI) y el consecuente calentamiento global (Al-Ghussain, 2019). Así, bajo un escenario de altas emisiones de GEI, la temperatura de la superficie global podría incrementar 2 °C en el año 2040 y hasta 5 °C en el 2100 con respecto a la temperatura del periodo 1850-1900 (IPCC, 2021). Ante esta situación, las zonas áridas se extenderán a una tasa de aproximadamente 115 km^2 por década y se intensificarán las altas y bajas temperaturas en todas las regiones climáticas (Cui et al., 2021).

Las altas temperaturas implican un desafío para la producción de carne ovina. El incremento de la Ta y la expansión de regiones cálidas afecta a la industria ovina de manera directa e indirecta (Sejian et al., 2014). Directamente, las altas temperaturas y mayor radiación solar ocasionan una disminución en el consumo de alimento, alteraciones en la función ruminal, compromiso del sistema inmune, así como mayor susceptibilidad a diferentes patógenos y enfermedades emergentes asociadas al cambio climático (Al-Dawood, 2017). Por otra parte, de manera indirecta, los ambientes cálidos ocasionan menor cantidad y calidad de alimento y agua generada por la escasez de lluvias, sequías y menor rendimiento de cultivos (Sejian et al., 2017). En conjunto, el estrés térmico y nutricional generado por estos factores causan una disminución en el bienestar y disponibilidad de nutrientes para las funciones biológicas en los ovinos (Marai et al., 2007). En última instancia, lo anterior se refleja en una menor fertilidad y tasa de crecimiento y, por lo tanto, en una menor producción de carne (Zhang et al., 2020). Sin embargo, es importante

mencionar que la severidad de estos impactos negativos dependerá del nivel de adaptación de cada tipo racial (McManus et al., 2020).

Los ovinos de pelo, al igual que ovinos de lana fina, son razas que han demostrado adaptarse a regiones con climas cálidos. En comparación con razas de lana media y lana larga provenientes de climas templados, los ovinos de pelo y productores de lana fina presentan una mayor capacidad de adaptación a altas temperaturas debido a las características morfológicas de talla, piel y cobertura de pelo o lana que han desarrollado como resultado de un proceso de selección natural y/o artificial (Kim et al., 2016). Así, como consecuencia de su origen y adaptación en climas cálidos, los ovinos de pelo presentan características fenotípicas tales como una mayor relación área de piel:peso vivo, menor grasa subcutánea mayor número de glándulas sudoríparas y una piel más delgada (Saraiva-Torres et al., 2017). Por su parte, ovinos de lana fina provenientes de zonas áridas o desérticas, tales como el Merino australiano, también han mostrado capacidad de adaptarse a condiciones climáticas desérticas debido a su menor talla corporal y menor longitud (< 75 micras) y diámetro (19 micras) de vellón con respecto a razas de lana media y larga (Alhidary et al., 2012; Wojtas et al., 2014). De este modo, las características fenotípicas mencionadas contribuyen a reducir el aislamiento térmico y hacer más eficientes los mecanismos de termorregulación de ovinos de pelo y lana fina, permitiéndoles crecer y reproducirse a pesar de las condiciones climáticas extremas (Macías-Cruz et al., 2016; McManus et al., 2020; Vicente-Pérez et al., 2020). Considerando lo anterior, dichas razas garantizan una producción constante de carne y, de este modo, contribuyen a la seguridad alimentaria en regiones de climas cálidos (Macías-Cruz et al., 2012).

2.3. Aclimatación de los ovinos de pelo al estrés por calor

2.3.1. Zona termoneutral e índices de estrés térmico

La zona termoneutral (ZT) es el rango de Ta en el cual los animales son capaces de equilibrar la producción y pérdida de calor corporal con un mínimo esfuerzo energético (Belhadj et al., 2016). En general, la ZT de los ovinos es de 12-

25 °C (Sejian et al., 2017); sin embargo, la edad, estado fisiológico, nivel de producción, genotipo y características físicas de lana/pelo son factores que afectan su umbral de tolerancia térmica (Nicolás-López et al., 2021b). Considerando el genotipo, la ZT de ovinos de pelo es de 15-30 °C debido a su mayor termorresistencia en comparación con razas de lana (Vicente-Pérez et al., 2020). Cuando la Ta está dentro de dichos límites, los animales se encuentran en un ambiente TN que les permite conservar su normotermia (Silanikove, 2000). Por el contrario, cuando la Ta excede el límite superior de la ZT, los ovinos de pelo experimentan EC, resultando críticas temperaturas ≥ 35 °C (Neves et al., 2009)

En ovinos, el índice más empleado para cuantificar el nivel de EC es el índice temperatura-humedad (ITH). De acuerdo con la fórmula empleada por Marai et al. (2007), los ovinos en general comienzan a experimentar EC a un ITH ≥ 22.2 unidades y este puede ser de tipo moderado (22.2 a <23.3), severo (23.3 a <25.6) y extremo-severo (≥25.6). Otra fórmula empleada en ovinos es la de Hahn (1999), la cual indica que el EC en razas de pelo comienza con un ITH ≥ 78 unidades (Macías-Cruz et al., 2016b). Sin embargo, es importante mencionar que las fórmulas propuestas por dichos autores no son de uso específico para ovinos, por lo cual se ha sugerido el desarrollo de índices exclusivos para la especie. En este sentido, Barbosa & Gomes (1995) establecieron el índice de confort térmico (ICT) para ovinos, con el cual se ha determinado que razas de pelo comienzan a sufrir EC a partir de un ICT ≥ 38 unidades (Neves et al., 2009). Por otra parte, algunos autores proponen el uso de variables fisiológicas para determinar el grado de EC. Basado en la puntuación de respiración/jadeo, Lees et al. (2019) clasifican el EC desde ausencia (0= frecuencia respiratoria [FR] normal y sin jadeo), hasta EC extremo (4= respiración y jadeo profundos, boca abierta y con la lengua completamente extendida). Por su parte, Seixas et al. (2017) demostraron que la FR y/o temperatura rectal (TR) pueden ser empleados para determinar los siguientes índices de tolerancia al calor (ITC) en ovinos de pelo: ITC= 100 - [(18 (TR) - 39.1)] o ITC= TR/FR + 39.1/27.

2.3.2. Mecanismos de termorregulación

En general, los ovinos son animales homeotermos, es decir, deben mantener constante una temperatura interna para el correcto funcionamiento de sus procesos fisiológicos (Al-Dawood, 2017). Para lograr lo anterior, los ovinos emplean diferentes mecanismos celulares, fisiológicos y metabólicos de termorregulación cuya activación depende del grado de EC ambiental (Gebremedhin, 2012). Bajo condiciones TN, los ovinos mantienen un equilibrio entre las pérdidas y ganancias de calor corporal a través del uso de mecanismos no evaporativos, los cuales no implican un gasto energético extra de mantenimiento (Macías-Cruz et al., 2018a). Sin embargo, en un ambiente de EC, estas razas hacen, en primera instancia, un esfuerzo por mantener su normotermia mejorando el funcionamiento de los mecanismos no evaporativos. Adicionalmente, si la severidad del estrés incrementa, los ovinos emplearán mecanismos evaporativos y metabólicos para mantener su normotermia (Macías-Cruz et al., 2016). La secuencia de eventos termorregulatorios que se presentan en ovinos según el nivel de EC se describe a continuación.

Cuando la Ta sobrepasa el límite superior de la ZT, los termorreceptores envían señales aferentes al sistema nervioso central. Dependiendo de la severidad del EC, el hipotálamo promueve la liberación de catecolaminas en fibras nerviosas simpáticas y, en segunda instancia, la activación del eje hipotálamo-hipófisis-adrenal para la liberación de cortisol (Collier et al., 2019). La consecuencia inmediata de la liberación de las catecolaminas (adrenalina y noradrenalina) consiste en redistribuir el flujo sanguíneo hacia la periferia para activar pérdidas no evaporativas de calor, mientras que el cortisol incrementa la disponibilidad de glucosa en torrente sanguíneo (Afsal et al., 2018). Como consecuencia de la redistribución del flujo sanguíneo, la radiación cutánea se convierte en la vía más importante de disipación de calor bajo EC ligero y moderado en ovinos de pelo, particularmente en aquellas regiones anatómicas altamente vascularizadas y en animales con mayor superficie de piel por kilogramo de peso vivo (Correa et al., 2012; Macías-Cruz et al., 2018ab). No obstante, a medida que se intensifican las condiciones de estrés, el gradiente térmico entre la piel del animal y el ambiente disminuye y con ello, la eficiencia de los mecanismos no evaporativos (Macías-Cruz et al., 2016). De tal modo que, en

condiciones de EC moderado a severo, los mecanismos evaporativos se vuelven esenciales para evitar la hipertermia (Gebremedhin, 2012).

Bajo condiciones de EC severo y extremo, los ovinos de pelo activan mecanismos fisiológicos adicionales de termorregulación. Inicialmente, la insuficiente disipación de calor por vías no evaporativas conlleva a la activación de mecanismos evaporativos, principalmente el aumento de la FR (Macías-Cruz et al., 2016) La evaporación respiratoria es la principal vía de pérdida de calor en razas de pelo, con la cual logran eliminar hasta el 90% de su carga total de calor corporal a partir de una Ta > 35 °C (Fonseca et al., 2017). El hecho de que estas razas incrementen su respiración hasta que disminuye el gradiente térmico, se debe a una adaptación conocida como heterotermia adaptativa. Este mecanismo fisiológico consiste en que, bajo condiciones severas de EC, los ovinos de pelo toleran una mayor carga de calor corporal durante las horas del día con mayor radiación solar (Vicente-Pérez et al., 2020). Así, al mantener menos tiempo una FR alta, se disminuyen los efectos colaterales de la evaporación respiratoria, es decir, alcalosis y un excesivo gasto energético e hídrico (Nicolás-López et al., 2021b). Adicionalmente, para evitar la deshidratación, los ovinos adaptados a climas cálidos disminuyen la pérdida de agua en heces y orina, consumen más agua e incrementan la reabsorción renal de electrolitos con acción osmótica (Piccione et al., 2012).

Si las condiciones de hipertermia persisten, los ovinos de pelo modifican su metabolismo post-absorción para disminuir la producción endógena de calor y garantizar el aporte de energía. La menor producción de calor metabólico es atribuida a una menor concentración sérica de hormonas tiroideas y la consecuente disminución de su actividad termogénica (Macías-Cruz et al., 2018b; Nicolás-López et al., 2021a). Por otra parte, la activación de vías de disipación de calor ocasiona una alta demanda de glucosa y oxígeno (O_2) en los tejidos. Como respuesta, los ovinos de pelo incrementan su sensibilidad a la insulina para garantizar el consumo celular de glucosa (Nicolás-López et al., 2021a). Asimismo, ante la presencia de lisis eritrocitaria asociada al EC (Correa et al., 2012), estas razas aumentan el tamaño celular y concentración de hemoglobina de los eritrocitos para garantizar un aporte constante de O_2 a las células (Reddy et al., 2019). En conjunto, a través de los

mecanismos de termorregulación mencionados, ovinos de pelo mayores a los 8 meses de edad mantienen su normotermia bajo condiciones de EC (Macías-Cruz et al., 2016, 2018b; Nicolás-López et al., 2021a). Sin embargo, en corderos de engorda y ovejas en lactancia, puede persistir un estado de hipertermia debido a la alta producción endógena de calor asociado al metabolismo del crecimiento y lactogénesis (Macías-Cruz et al., 2018b).

2.3.3. Respuesta celular y estrés oxidativo

Las respuestas de aclimatación que presentan los ovinos termorresistentes son regulados por una compleja red de genes (McManus et al., 2020). Estudios de secuenciación y polimorfismos del genoma de ovejas nativas de climas cálidos han permitido identificar genes candidatos de termorresistencia (Lv et al., 2014). Considerando aspectos morfológicos, algunos de estos genes están involucrados con la pigmentación del pelo (ASIP, MC1R y TRYP1) y piel (FGF2, GNAB y PLCB1), protección epidérmica (F13A1), deposición muscular (MSTN, BMP7, NPR2 y LEP) y talla corporal pequeña (DIS3L2, PLAG1, NIPB1, BMP2, BMP4 y GJB2) (Chauhan et al., 2014a; Berihulay et al., 2019; Luna-Nevarez et al., 2020; McManus et al., 2020). Por otra parte, también se han identificado genes asociados con la actividad del ácido araquidónico (ANXA6, GPX3, GPX7 y PTGS2), sistema renina-angiotensina (CPA3, CPVL y ECE1), oxitocina (CALM2, CACNA2D1, KCNJ5 y COX2) y prolactina (PRL), sustancias que se asocian con el mantenimiento del balance hídrico (Yang et al., 2016; Abousoliman et al., 2020). Asimismo, algunos autores sugieren que el estado energético en ovinos termorresistentes es mediado por genes que regulan la gluconeogénesis (VNN1 y NR1H3), secreción pancreática (RAP1A, SLC4A4, CPA3 y CPB1), actividad tiroidea (TSRH) y la activación de GTPasas (TBC1D12) (Lv et al., 2014; Yang et al., 2016; Li et al., 2019; Luna-Nevárez et al., 2021). De manera conjunta, estos genes interactúan para proveer a los ovinos una mayor tolerancia térmica, por lo cual representan una importante herramienta para selección de animales aptos para la producción en climas cálidos.

Por otra parte, el EC altera la síntesis de proteínas y ocasiona la formación de agregados proteicos no funcionales que comprometen la viabilidad celular (Belhadj et al., 2016). Para contrarrestar lo anterior, la célula incrementa la expresión de proteínas de choque térmico (HSPs) inducibles para disminuir el daño celular y, por lo tanto, adquirir mayor termorresistencia (Archana et al., 2017). No obstante, esto último aún resulta controversial ya que, mientras algunos autores asocian una mayor expresión de HSPs con una mejor respuesta termorregulatoria (Gupta & Mondal, 2019), otros sugieren que una mayor expresión de estas proteínas es indicativa de mayor daño celular como consecuencia de fallas en los mecanismos de termorregulación (Singh et al., 2017). En ovinos, Romero et al., (2013) asociaron una mayor viabilidad celular de células mononucleares y menor TR en ovejas Pelibuey estresadas por calor con una mayor expresión de HSP70. En congruencia con lo anterior, al comparar la concentración sérica de HSP70 y capacidad de termorregulación en diferentes razas de pelo nigerianas, Akinyemi et al. (2019) también observaron una menor TR en razas que presentaron concentraciones más altas de HSP70. Por el contrario, Singh et al. (2017) asociaron una menor expresión de HSP90 con una mayor capacidad de termorregulación en ovinos de pelo de la raza Madras Red. En este sentido, se requieren más estudios que permitan esclarecer si los individuos mejor adaptados a los climas cálidos producen concentraciones altas o bajas de HSPs.

El EC induce un estado de estrés oxidativo, que se caracteriza por una sobreproducción de radicales libres e insuficiente defensa antioxidante (Belhadj et al., 2016). De acuerdo con Belhadj et al. (2019), la Ta e ITH se correlacionan positivamente con el índice de estrés oxidativo (IEO) de ovinos; sin embargo, los mecanismos moleculares implicados aún no han sido explicados en esta especie. Informes en otros animales estresados por calor sugieren que la excesiva producción de radicales libres se debe a la reacción del O_2 celular con electrones que escapan de la cadena de transporte de electrones y con metales de transición acumulados, principalmente el hierro (Chauhan et al., 2014a; Akbarian et al., 2016; Belhadj et al., 2016). A partir de dichas reacciones se forman el radical superóxido y el peróxido de hidrógeno (H_2O_2) que, tras una serie de reacciones secuenciales, dan origen a otras

especies reactivas de oxígeno (ROS) (Belhadj et al., 2014). Posteriormente, debido a su alta inestabilidad, los ROS reaccionan con las diferentes biomoléculas celulares alterando su integridad estructural y funcional (Akbarian et al., 2016). Aunado a lo anterior, la hipoxia asociada a la vasoconstricción vascular en órganos internos (Sejian et al., 2017), así como el acelerado metabolismo que ocasiona la FR (Belhadj et al., 2019), son factores que también contribuyen a incrementar el daño oxidativo en ovinos.

La información disponible hasta el momento confirma la presencia de daño oxidativo en ovinos de pelo estresados por calor. Shi et al. (2020) reportaron en corderos Dorper x Mongolian que el EC disminuye la concentración sérica de las enzimas antioxidantes catalasa, glutation peroxidasa (GPx) y superóxido dismutasa (SOD) y aumenta la concentración de malondialdehído (MDA). Esto concuerda con lo demostrado por Wang et al. (2019b), quienes asociaron en corderos Dorper x Han una menor capacidad antioxidante total con un ambiente cálido. El grado de daño oxidativo en ovinos de pelo bajo EC puede depender de la severidad del estrés, genotipo y disponibilidad de agua. Valadez-García (2019) observó en corderas Dorper x Pelibuey estresadas por calor una menor capacidad antioxidante total y mayor concentración sérica de biomarcadores de oxidación lipídica y proteica conforme incrementaba la Ta. Por otra parte, ovinos de la raza Uda presentaron una menor TR y mayor capacidad antioxidante que ovinos de otras razas de pelo con menor termorresistencia (Okeke et al., 2020). Finalmente, ovejas Pelibuey expuestas a EC ambiental y restricción de agua presentaron menor actividad de las enzimas catalasa y SOD en eritrocitos que animales expuestos únicamente a estrés térmico (Serrano et al., 2021). En general, estos estudios muestran que, a pesar de que los ovinos de pelo bajo EC logran restablecer su normotermia, también son sensibles a presentar daño oxidativo.

2.4. Efecto de estrés por calor sobre la producción de carne de ovinos de pelo

El EC compromete la producción de proteína de origen animal; sin embargo, en ovinos de pelo, el daño en la producción de carne no es severo (Vicente-Pérez et

al., 2020). Durante la engorda, las altas Ta ocasionan una disminución en la tasa de crecimiento y eficiencia alimenticia de ovinos de pelo, sin afectar su consumo de alimento. En corderos Dorper x Katahdin, Macías-Cruz et al. (2020) reportaron una disminución de más del 25% en la GDP y eficiencia alimenticia, respuesta que fue asociada a un incremento del 32% en los gastos energéticos de mantenimiento (Nicolás-López et al., 2021b). Por otra parte, reportes generados hasta el momento en corderos Dorper (Aleena et al., 2020; Zhang et al., 2021) y sus cruzas con Katahdin (Macías-Cruz et al., 2020) y Pelibuey (Macías-Cruz et al., 2013), demuestran que el EC no afecta la ingesta de materia seca en razas de pelo, lo cual es atribuido a su capacidad de aclimatación a los ambientes cálidos. La falta de efecto del EC en el consumo de alimento representa una ventaja energética importante para estas razas al garantizar la disponibilidad de nutrientes para su termorregulación y, aunque en menor medida, continuar creciendo (Nicolás-López et al., 2021a).

El mantenimiento de los niveles de consumo de alimento evita que los ovinos de pelo movilicen tejido adiposo y muscular y, por el contrario, les permite mantener un ambiente de anabolismo lento y metabolismo post-absortivo que se refleja en la ganancia de peso continua y en el mantenimiento de los atributos de canal (Aleena et al., 2020; Macías-Cruz et al., 2018c; 2020). En general, la exposición corta (14 d) o prolongada (>30 d) de corderos de pelo a EC no afecta el peso, rendimiento y conformación de la canal, así como en la deposición de grasa corporal (Macías-Cruz et al., 2013; 2020; Zhang et al., 2021). Contrario a lo esperado, Macías-Cruz et al. (2013; 2020) reportaron un aumento del 5% en el rendimiento de la canal caliente y del 35% en el área del ojo de la costilla en corderos de pelo bajo EC ambiental, efectos que pudieron estar mediados por un incremento en la sensibilidad a la insulina y resistencia al cortisol en el músculo esquelético (Macías-Cruz et al., 2020; Nicolás-López et al., 2021a). Con respecto a la deposición de grasa, el EC no afecta el total de grasa interna en ovinos de pelo, pero sí ocasiona una redistribución de ésta al aumentar en la región pélvica-renal-corazón (KPH) y disminuir en la zona omental (Macías-Cruz et al., 2020). Los autores sugirieron que la menor cantidad de grasa omental puede ser una adaptación para facilitar la disipación del calor

generado por la actividad ruminal, mientras que el aumento de grasa KPH, dada su alta vascularización, garantiza una rápida disponibilidad de energía en caso de déficit nutricional.

El EC ha sido asociado con una alta incidencia de carne oscura, firme y seca en ovinos debido a un agotamiento en las reservas de glucógeno muscular durante la engorda y, consecuentemente, a un pH final ≥ 6 en la carne (Gonzalez-Rivas et al., 2020; Zhang et al., 2021). No obstante, información disponible hasta el momento en carne de razas de pelo demuestra que, a pesar de que el EC disminuye la capacidad de retención del agua e incrementa el pH final, luminosidad, tono, intensidad de color, saturación y esfuerzo al corte, estos atributos se mantienen dentro de los valores de referencia sin presentar detrimentos en la calidad (Macías-Cruz et al., 2020; Zhang et al., 2021). De hecho, los valores altos en los parámetros de color son indicativo de una carne más brillante y atractiva para el consumidor. De acuerdo con Macías-Cruz et al. (2020), esto puede estar asociado con la termorresistencia de estas razas y con un posible aumento de fibras musculares tipo IIa caracterizadas por su menor susceptibilidad al estrés por calor, alto contenido de mioglobina, buena actividad aeróbica y alto contenido de glucógeno. Sin embargo, esta última hipótesis aún requiere ser confirmada.

En conjunto, los estudios mencionados demuestran que las altas Ta no son un factor que afecte negativamente la producción de carne en ovinos de pelo. Si bien, el EC ocasiona una dismnución en la GDP y eficiencia alimenticia debido a una menor disponibilidad de energía para el crecimiento, esto es parcialmente compensado por el mantenimiento del consumo de alimento y ajustes en el metabolismo post-absortivo. Por consiguiente, el establecimiento de estrategias que ayuden a reforzar dichas respuestas, permitirá incrementar la eficiencia de los ovinos de pelo en la producción de carne bajo EC.

2.5. Estrategias nutricionales para mitigar el EC en la engorda de ovinos

La reducción en la tasa de crecimiento debido al EC en ovinos de pelo representa un área de oportunidad para el desarrollo de tecnologías que permitan

parcial o totalmente mitigar dicho efecto negativo del EC en la producción de carne ovina. Considerando que el consumo de alimento no es afectado por las altas Ta, la manipulación de la alimentación de los ovinos de engorda estresados por calor podría ser una alternativa de mitigación al cubrir necesidades nutricionales específicas extras de mantenimiento. En este sentido, actualmente se puede encontrar una amplia variedad de estudios que buscan mejorar el crecimiento y las características de la canal de los ovinos de engorda en ambientes cálidos a través de incrementar la densidad energética, proteica, o la inclusión de aditivos dietarios (Sejian et al., 2017; Conte et al., 2018).

2.5.1. Cambios en el manejo de alimentación

Modificaciones simples y económicas en los programas de alimentación pueden ayudar a los ovinos a disminuir su carga de calor corporal y a mejorar la disponibilidad de energía para crecimiento (Chagas et al., 2015). En general, todos los ovinos bajo EC tienden a disminuir su consumo de alimento y pasar más tiempo echados durante las horas de mayor radiación solar. No obstante, las razas de pelo compensan dicha disminución en el consumo de alimento incrementándolo drásticamente por las noches y las mañanas, lo que lleva finalmente a que el consumo promedio diario sea similar al presentado en condiciones TN (Li et al., 2018). Considerando lo anterior, el proporcionar alimento de calidad durante las horas más frescas del día, o bien, con una mayor frecuencia, han sido estrategias que disminuyen el calor metabólico generado por la ingesta de alimento en las horas más cálidas del día (Renaudeau et al., 2012). En este sentido, Chagas et al. (2015) observaron en corderos Santa Inés que la FR y TR disminuyen al cambiar la hora de alimentación de la tarde, siendo mejor a las 18:00 h que a las 15:00 h. Por su parte, Abozed et al. (2021) demostraron en corderos finalizados en las condiciones áridas de Egipto que alimentar tres veces al día (08:00, 13:00 y 18:00 h) incrementa la GDP y disminuye la TR con respecto a los animales alimentados solamente dos veces al día (08:00 y 13:00 h). Otras prácticas de manejo que favorecen la ingesta de una mayor cantidad de alimento en ambientes cálidos son la colocación de comederos y

bebederos bajo la sombra, así como ofrecer productos dietéticos y agua de calidad (Sejian et al., 2017).

2.5.2. Modificación nutricional de la dieta

El aumento en la densidad energética en la dieta ha demostrado ser una estrategia de mitigación del EC con resultados consistentes en ovinos de engorda. Esto se asocia a que dichos animales requieren una mayor cantidad de energía disponible para mantenimiento, la cual generalmente es obtenida de la energía dietaria destinada para crecimiento, o bien del catabolismo del tejido graso o muscular (Mahjoubi et al., 2015). Tradicionalmente, una práctica para aumentar la densidad energética de las dietas de engorda consiste en aumentar la inclusión de carbohidratos fermentables (Conte et al., 2018). Sin embargo, debido a que este tipo de dietas incrementa la producción endógena de calor y el riesgo de alteraciones ruminales (Sejian et al., 2017), actualmente se evalúa la suplementación de fuentes alternas de energía y compuestos gluconeogénicos en corderos bajo EC. Halakoo et al. (2020) demostraron en corderos de lana estresados por calor que la adición dietaria de grasa de sobrepaso, cebo de res o aceite de canola disminuye tanto TR y FR, al mismo tiempo que incrementa la concentración sérica de glucosa. Por otra parte, la adición dietaria de precursores gluconeogénicos incrementa el consumo de alimento y disminuye la TR en corderos Afshari expuestos a EC (Mahjoubi et al., 2016). En congruencia con lo anterior, Sejian et al. (2017) mencionan que la producción de carne ovina en climas cálidos puede mejorar al emplearse compuestos capaces de aumentar la liberación de insulina y la acción de ésta sobre los tejidos.

Adicional al incremento de energía, otros ajustes en la dieta para ovinos estresados por calor consisten en disminuir la cantidad de fibra y evitar un exceso de proteína. Ovinos alimentados con dietas altas en fibra presentan una mayor producción de calor metabólico asociado a niveles más altos de acetato ruminal (Sejian et al., 2017). Por otra parte, si la energía es limitante, un porcentaje de inclusión de proteína similar o mayor al que se provee bajo condiciones TN

incrementa el gasto energético de mantenimiento para eliminar el exceso de N en forma de urea (Conte et al., 2018). Considerando lo anterior, corderos sometidos a EC deben ingerir dietas con un bajo porcentaje de fibra detergente neutro y garantizar una mayor densidad energética antes que un mayor aporte de proteína (Marai et al., 2007; Al-Dawood, 2017). No obstante, bajo dichas condiciones ambientales, los requerimientos de fibra y la relación proteína-energía de estas razas aún no han sido establecidos.

2.5.3. Suplementación de antioxidantes

El EC genera una mayor producción de ROS y menor poder antioxidante, por lo cual la adición dietaria o administración directa en el cuerpo de antioxidantes es una estrategia que puede beneficiar el crecimiento de los corderos estresados por calor (Chauhan et al., 2021). Actualmente, existe evidencia sobre un mejor crecimiento, metabolismo y capacidad de termorregulación por efecto de incluir en la dieta o administrar intramuscularmente vitaminas, minerales y fitoquímicos con acción antioxidante en los ovinos. No obstante, los resultados benéficos a través de los estudios no son consistentes, ya que mientras unos reportan mejoras (Chauhan et al., 2014ab; 2015; 2016), otros no han encontrado efecto alguno (Alhidary & Abdelrahman, 2014, 2016).

En corderos de lana sometidos a EC, la suplementación con dosis suprafisiológicas de vitamina E + Se disminuyó el IEO y aumentó la respuesta antioxidante celular, lo cual se relacionó con la acción anti-peroxidación lipídica de la vitamina E y al hecho de que el Se favorece la acción de la enzima GPx (Chauhan et al., 2014ab). Adicionalmente, en el músculo esquelético, ambos antioxidantes modularon la expresión de HSP70, citoquinas proinflamatorias y del factor de transcripción NF-kB, disminuyendo el daño oxidativo generado por el EC en los ovinos (Chauhan et al., 2014b). Lo anterior, en conjunto, se reflejó en beneficios biológicos y productivos, tales como mejoras en la capacidad de termorregulación, PV final, rendimiento de la canal y estabilidad lipídica de la carne durante su

almacenamiento (Alhidary et al., 2015; Chauhan et al., 2014 ab; 2015; 2016; 2020). Sin embargo, en razas de pelo, el conocimiento de esta estrategia es incipiente.

Por otra parte, algunos fitoquímicos han generado interés científico sobre su posible utilidad para aumentar la producción ovina de razas lanares en ambientes cálidos, debido a su potente actividad antioxidante (Lee et al., 2017). Así, algunos estudios en corderos de lana estresados por calor evidenciaron que los compuestos fenólicos y carotenoides mejoran los parámetros productivos debido al poder reductor y a la capacidad para estimular las respuestas enzimáticas antioxidantes que poseen dichos compuestos (Liu et al., 2016; Jiang et al., 2019). En corderos Awassi expuestos a una Ta de 38.5 °C, la suplementación con 1.0 y 7.0 g de naringina aumentó la GDP, eficiencia alimenticia y peso vivo final, atribuyéndolo a una mayor actividad en las enzimas SOD y GPx, así como a una mayor concentración sérica de albúmina e inmunoglobulinas (Alhidary & Abdelrahman, 2014, 2016). Similares resultados enzimáticos, inmunológicos y de crecimiento fueron reportados en corderos de lana de raza Hu estresados por calor cuando se suplementaron con extracto de cúrcuma (compuesto rico en fenoles; Jiang et al., 2019). Por su parte, Liu et al. (2016) reportaron que la suplementación de taninos en corderos de lana Ujumqin durante la época de verano, mejoró la respuesta antioxidante general y en el tejido hepático y muscular, favoreciendo una mayor GDP (13 %) y eficiencia alimenticia (14 %). Finalmente, tanto los taninos (Liu et al., 2016) como el carotenoide licopeno (Jiang et al., 2015) han resultado eficaces en evitar la peroxidación lipídica y mantener estabilidad en el color de la carne fresca de corderos de lana expuestos a insulto térmico. En conjunto, los resultados mencionados evidencian que la adición dietaria de fitoquímicos con propiedades antioxidantes es una buena estrategia nutricional para mejorar la producción de carne de corderos bajo escenarios de EC; sin embargo, en corderos de pelo estresados por calor, no se encontró información al respecto.

2.6. El grupo fenólico de los ácidos hidroxicinámicos

Los compuestos fitoquímicos con propiedades nutracéuticas en la alimentación animal han sido motivo de una gran cantidad de estudios en la última década, destacando la extensa información que hay sobre los compuestos fenólicos, los cuales son los más abundantes en la naturaleza (Liu, 2013). Los fenoles son un grupo bastante heterogéneo de metabolitos secundarios cuya función en las plantas consiste en proveer protección contra agentes físicos y patógenos, mientras que en humanos y animales ejercen múltiples mecanismos de acción con implicaciones nutracéuticas (de Paiva et al., 2013; Guan et al., 2021). Cabe mencionar que los ácidos hidroxicinámicos (AH) son el grupo de fenoles con más beneficios demostrables para la salud, crecimiento y bienestar de los animales (Kumar & Goel, 2019). En este sentido, su uso en la alimentación animal representa una estrategia natural y sostenible para mejorar la producción de carne sin comprometer la seguridad y salud del consumidor (Peña-Torres et al., 2019; Serra et al., 2021).

2.6.1. Generalidades

Los AH se localizan naturalmente en la pared celular de verduras, frutas, granos y cereales (Kumar & Goel, 2019), por lo que forman parte de la dieta diaria de los animales de producción. No obstante, sus efectos benéficos en la salud y crecimiento de los animales son poco evidentes cuando se encuentran formando parte de la matriz de la pared celular; de ahí la importancia de ofrecerlos en forma libre (Serra et al., 2021). Actualmente, se han desarrollado diferentes métodos de extracción de estos compuestos fenólicos y muchos de ellos están disponibles comercialmente.

Los AH se sintetizan en la vía del shikimato y poseen una estructura base fenilpropanoide C6-C3 a la que se une uno o más grupos hidroxilo (OH) y un grupo carboxilo (COOH) en la cadena lateral (Taofiq et al., 2017). El número y la posición de los grupos OH determina el AH que se produce, destacando por su abundancia en la naturaleza el ácido ferúlico, p-cumárico, cafeico y cinámico (Figura 1). En la pared celular vegetal, los AH se encuentran principalmente unidos a péptidos,

hidroxiácidos o glucósidos y, en menor medida, en su forma libre. Dicha disposición de los AH en las plantas determina su biodisponibilidad en los humanos y animales que los ingieren (Sova & Saso, 2020).

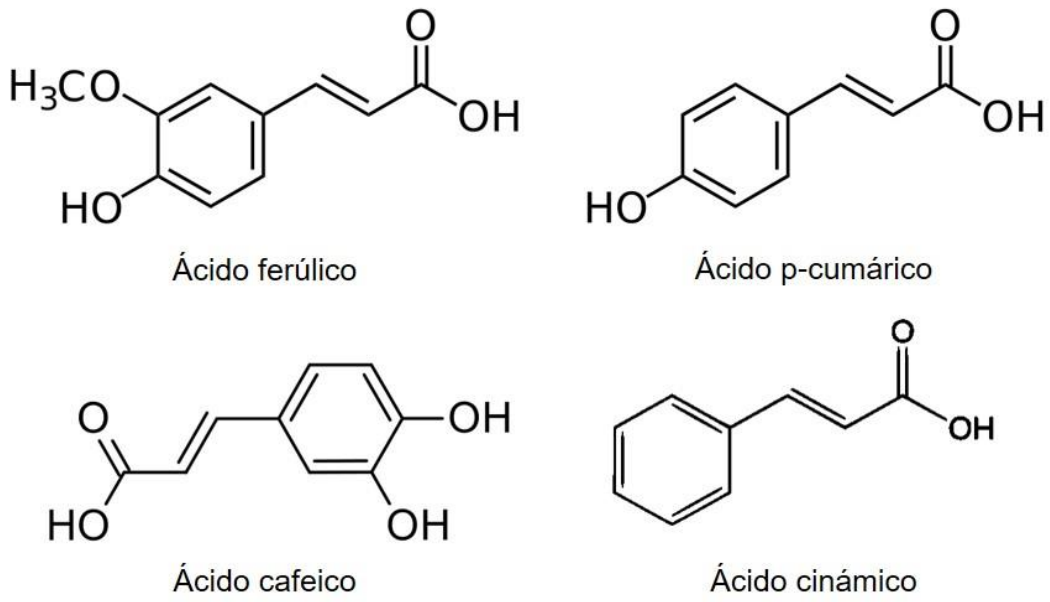

Figura 1. Ácido hidroxicinámicos más abundantes en la naturaleza.

Cuando forman parte de la matriz del alimento ingerido, solo una pequeña porción de los AH unidos a la pared celular son liberados por enzimas y microorganismos del tracto gastrointestinal (TGI) para posteriormente ser absorbidos en intestino delgado, metabolizados en hígado y excretados vía renal (Mancuso & Santangelo, 2014; Zhao & Moghadasian, 2008). Por su parte, los AH que no son liberados de la matriz del alimento continúan su paso en el TGI y se pierden por vía fecal (Peña-Torres et al., 2019). No obstante, cuando los AH son extraídos de las plantas por métodos enzimáticos o alcalinos e ingeridos en su forma libre, la mayor parte es rápidamente absorbida en estómago e intestino delgado por difusión simple y/o transporte activo, escapando así de la acción enzimática y microbiana (Adam et al., 2002; Chesson et al., 1999). Así, al ser más biodisponibles para los diferentes tejidos, los AH libres ejercen de manera más eficaz sus efectos biológicos nutracéuticos.

2.6.2. Propiedades nutracéuticas

Los AH son compuestos bioactivos nutracéuticos al mejorar la salud y reducir el riesgo de contraer enfermedades tanto en humanos como en animales (Bobeck, 2020). Los beneficios biológicos que llevan a cabo estos fenoles son muy variados, ya que tienen el potencial para reducir el estrés oxidativo, actuar como citoprotectores de células y tejidos, modular el metabolismo, ejercer acciones antimicrobianas y antinflamatorias, mejorar el sistema inmune, y trabajar como promotor de crecimiento de tipo prebiótico o por acción directa a nivel de fibras musculares (Kumar & Goel, 2019; Peña-Torres et al., 2019; Valenzuela-Grijalva et al., 2021). Los mecanismos de acción por los cuales los AH promueven estas propiedades nutracéuticas en animales y humanos son diversos y a continuación se enlistan:

1. Actúan como agentes reductores al transferir átomos de hidrógeno o electrones y estimulan la expresión de enzimas antioxidantes al activar la vía del factor nuclear eritroide similar al factor 2/elemento de respuesta antioxidante (Nrf2/ARE; Abramovič, 2015).
2. Ejercen mecanismos bactericidas y bacteriostáticos, además de que inhiben la replicación viral (Sova & Saso, 2020).
3. Inhiben la expresión de factores que desencadenan la inflamación (FNT-α, IL-6 y NF-κB; Bobeck, 2020).
4. Tienen acciones hipolipemiantes al inhibir las enzimas implicadas en la biosíntesis de colesterol y triglicéridos, al mismo tiempo que aumentan la β-oxidación hepática (de Oliveira Silva & Batista, 2017).
5. Ejercen un efecto hipoglucemiante de manera directa al mejorar la defensa antioxidante de las células β-pancreáticas y la translocación de GLUT4 en los tejidos, e indirectamente al disminuir la absorción intestinal de glucosa, incrementar la expresión de la glucógeno sintasa e inhibir la acción de la glucosa-6-fosfatasa (García-Cordero et al., 2020).
6. Estimulan la activación de vías celulares y expresión de diferentes genes implicados en la diferenciación, hipertrofia y defensa antioxidante del

músculo esquelético (Chodkowska et al., 2018; Chen et al., 2019; Kuppusamy et al., 2019; Wang et al., 2021).

7. Modulan la microbiota intestinal al servir como sustrato de bacterias benéficas (familias *Bifidobacteriaceae* y *Lactobacillaceae*) y ejercer su actividad antimicrobiana sobre bacterias patógenas (*familia Enterobacteriaceae*) (Gong et al., 2019; Nazzaro et al., 2020; Plamada & Vodnar, 2022).

2.6.3. Uso en la producción de carne ovina

Hasta el momento, el AF es el único hidroxicinamato evaluado en la producción de carne debido a sus múltiples propiedades bioactivas (Serra et al., 2021). En ovinos, al igual que en bovinos, el poder antioxidante del AF parece ser el encargado de generar efectos positivos en el crecimiento y deposición muscular bajo situaciones de estrés térmico-oxidativo (Macías-Cruz et al., 2014; Flores-Campos et al., 2015; González-Ríos et al., 2016; Wang et al., 2019ab; Peña-Torres et al., 2020). Sin embargo, en ausencia de condiciones estresantes, éste compuesto fenólico parece no actuar en pro de una mayor producción de carne ovina (Soberon et al., 2012; Macías-Cruz et al., 2014; Ortega-Flores et al., 2015),

En condiciones TN, la suplementación de AF en corderos de lana y de pelo no generó cambios en parámetros productivos y de la canal (Soberon et al., 2012; Macías-Cruz et al., 2014; Ortega-Flores et al., 2015). No obstante, en corderos Dorper x Han, la suplementación de AF libre en condiciones de estrés por frío o de feruloil oligosacáridos (derivado del AF) bajo EC moderado, incrementó la GDP y la eficiencia alimenticia como resultado de una mayor respuesta enzimática antioxidante (Wang et al., 2019ab). Con respecto a la calidad de la carne, si bien el AF ha mostrado no afectar las características fisicoquímicas del músculo *Longissimus thoracis* de corderos de pelo finalizados en condiciones TN, sí ha sido evidente un aumento en el tamaño de las fibras musculares oxidativas por efecto de dicho fenol (Peña et al., 2018). En conjunto, los hallazgos mencionados sugieren que los AH, particularmente el AF, mejoran el crecimiento de ovinos de engorda al actuar

como antioxidante en presencia de un factor estresante y, posiblemente, en aquellos tejidos con un alto metabolismo aeróbico.

2.7. Producción de carne de ovinos de pelo en climas cálidos: Uso del ácido ferúlico

En la literatura no se encontraron estudios donde hayan evaluado el efecto del AF en ovinos estresados por calor; no obstante, al considerar las múltiples propiedades bioactivas que ejerce este compuesto, se puede especular su utilidad para mejorar la producción de carne ovina en ambientes cálidos. El AF podría mejorar el crecimiento de corderos de pelo bajo EC al disminuir el estrés oxidativo. Esto es sugerido al observar que, tanto en corderos estresados por frío (Wang et al., 2019a) como en bovinos estresados por calor (Peña-Torres et al., 2020), la suplementación con AF libre incrementa la GDP, eficiencia alimenticia y deposición muscular como resultado de una mayor defensa enzimática antioxidante. Adicionalmente, algunos estudios *in vivo* e *in vitro* han demostrado que el AF revierte el daño oxidativo en el hígado (Li et al., 2015), páncreas (Wang et al., 2015), eritrocitos (Ma et al., 2011) e intestino delgado (He et al., 2016; 2018; Chen et al., 2021). De presentarse dichos efectos en corderos de pelo estresados por calor, el AF podría mejorar la absorción intestinal, gluconeogénesis hepática y el aporte de glucosa y O_2 a los tejidos, incrementando así la disponibilidad de nutrientes y energía para el crecimiento.

Por otra parte, el AF podría mejorar la deposición muscular y calidad de la carne al ejercer diferentes mecanismos de acción sobre el músculo esquelético. En cerdos, estudios recientes demuestran que el AF favorece el desarrollo de fibras glucolíticas (Valenzuela-Grijalva et al., 2021) y oxidativas (Wang et al., 2021) como resultado de un posible efecto β-adrenérgico y a la activación de la vía Sirt/AMPK/PGC-α, respectivamente. Asimismo, otros estudios señalan que el AF promueve el anabolismo en el tejido muscular al aumentar la sensibilidad a la insulina (Ghosh et al., 2017) y la resistencia a la fatiga (You et al., 2009), así como al mejorar la expresión de genes asociados a la miogénesis (*Myod* y *Myog*),

crecimiento (*Igf1r*), respuesta antioxidante (*Nrf2*) y actividad antiapoptótica (*Igfr2*; Wen & Ushio, 2017; Chodkowska et al., 2018). Finalmente, después del sacrificio, se ha reportado que el AF retarda la oxidación de lípidos y mioglobina en el músculo de cerdos (Li et al., 2015) y bovinos (González-Ríos et al., 2016). Con base a la información mencionada, el AF podría representar una opción viable para incrementar la deposición muscular y mejorar la calidad de la carne de ovinos de pelo bajo EC ambiental. Sin embargo, se requiere que los posibles efectos aquí planteados sean comprobados.

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CAPÍTULO III. ARTÍCULOS

3.1. Ferulic acid in animal feeding: Mechanisms of action, productive benefits, and future perspectives in meat production

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3.1.1. Abstract

The livestock sector's major challenge is to meet the growing demand for foods of animal origin without compromising animal welfare and human health. In this effort to produce more efficiently and ethically, researchers have currently been focused on the study of phytochemicals with nutraceutical properties in order to improve meat production. Ferulic acid (FA) is a phenolic compound that is attracting special interest in the livestock sector due to its multiple benefits associated with its antioxidant, cytoprotective, antimicrobial, and anabolic properties. The activation of these mechanisms stimulates and/or favors physiological and metabolic processes, and consequently, farm animals' growth and reproduction. Thus, FA ingestion could improve feedlot performance, carcass characteristics, and meat quality, as well as gonad-gamete activity. However, the information available is controversial. Therefore, this review aimed to summarize current information about the mechanisms of action of FA and its benefits on productive and reproductive aspects, highlighting new possible applications of this phytochemical in the meat production chain.

Keywords: Phytochemicals, Phenolic compounds, Hydroxycinnamates, Antioxidants, Anabolism, Meat production.

3.1.2. Introduction

According to projections, the world population will reach 9.1 billion people in 2050; it will also increase the demand for animal-source foods by approximately 75% (Baldi & Gottardo, 2017). In this context and under the approach of a "clean, green and ethical" production (Sneddon, 2009) the current animal production systems must guarantee food safety without compromising both animal welfare and human health (Lillehoj et al., 2018). As a result, a natural strategy to increase animal protein production is the use of phytochemicals with nutraceutical properties instead of synthetic antimicrobials, growth promoters, or hormones (Hashem, González-Bulnes & Simal-Gandara, 2020; Macías-Cruz et al., 2018; Marquardt & Li, 2018).

Phytochemicals are bioactive compounds produced during the plant metabolism that can improve animal productivity by exerting different mechanisms of

action (Kumar & Goel, 2019). The most abundant phytochemicals are hydroxycinnamic acids, phenolic compounds with powerful antioxidant activity that favorably mediate different physiological and metabolic processes (Peña-Torres et al., 2019). Currently, the ferulic acid (FA) is a phenol of special interest in the livestock sector since its antioxidant, antimicrobial, and anabolic properties may generate health, productive, and reproductive benefits in farm animals (González-Ríos et al., 2016; Li et al., 2015; Macías-Cruz et al., 2018; Valadez-García et al., 2021; Wang, Wang, et al., 2019).

The dietary supplementation of FA in fattening animals increases muscle deposition and feed efficiency (Herrera, Alejo, & Asaff, 2011; Valadez-García et al., 2021; Wang, Wang, et al., 2019b), and improves meat quality and shelf life (González-Ríos et al., 2016; Li et al., 2015). Concerning reproductive efficiency, FA induces endocrine and exocrine activity in gonads, reproductive tract development (Macías-Cruz et al., 2018; Moshfegh, Baharara, Namvar, Zafar-balanezhad, & Amini, 2016), *in vitro* maturation, fertilization of oocytes (Lee & Hyun, 2017; Tanihara et al., 2018) and semen cryopreservation (Affonso et al., 2017). However, in some cases, the benefits described as an effect of FA across the literature are sometimes inconsistent (González-Ríos et al., 2016; González-Ríos, Gil, & Berrondo, 2013; Li et al., 2015; Macías-Cruz et al., 2014). Therefore, this review aimed at summarizing current information about the mechanisms of action of FA and its benefits on productive and reproductive aspects, highlighting new possible applications of this phytochemical in the meat production chain.

3.1.3. Generalities and importance as a functional ingredient

The FA is the most abundant phenolic compound from the group of hydroxycinnamates and is found as part of the cell wall of plants, fruits, vegetables feedstuffs and cereal grains (Cao, Jin, Yang, Li, & Jiang, 2015; de Paiva, Goldbeck, Dantas, & Squina, 2013). This phenol was first isolated from *Ferula foetida* in 19th century and chemically described in 1925 (de Oliveira Silva & Batista, 2017). The FA [(E) -3- (4-hydroxy-3-methoxy-phenyl) propyl-2-enoic acid] presents *cis*- and *trans*-

isomerism being the *cis*-isomer a yellow oily liquid and the *trans*-isomer (the most abundant in nature) a white crystal (de Paiva et al., 2013; Kuppusamy, Soundharrajan, Kim, Hwang, & Choi, 2019). Overall, it is soluble in water, ethyl acetate, ethanol, and ethyl ether, sensible to isomerization by sunlight (Bento-Silva, Vaz, & Bronze, 2018), and has a melting point of 168–171 ◦C and molar mass of 194,186 g mol 1 (National Center for Biotechnology Information, 2019).

In plants, FA is a secondary metabolite synthesized in the shikimate/ phenylpropanoid pathway to give stiffness and protection (de Oliveira Silva & Batista, 2017). So, it is part of the cell wall's structural composition where is found free, dimerized and linked by ester and ether bonds with lipids, carbohydrates and lignin (de Paiva et al., 2013). Both free and bound FA can be released from natural sources by different extraction methods (Mancuso & Santangelo, 2014). While free FA needs aqueous or organic solvents to be extracted (e.g., methanol), bound FA requires chemical alkaline or enzymatic hydrolysis treatments to break covalent bonds with the other cell wall components. Depending on the extraction method and operating conditions (e.g., room temperature, pH, and time), free FA or different bioactive derivatives can be released (Bento-Silva, Vaz Patto, & do Rosario Bronze, 2018).

The FA is a functional ingredient because it has beneficial effects on human health associated with its antioxidant action (Kumar & Pruthi, 2014; Kuppusamy et al., 2019). Thus, this phenol acts as an anti-inflammatory, hepatoprotective, antidiabetic, anticholesterolemic, anticancer, neuroprotective, and UV protector agent (de Oliveira Silva & Batista, 2017). Furthermore, studies in murine models suggest that FA may be useful to treat obesity and infertility in humans (Kuppusamy et al., 2019; Salazar-López et al., 2017). In addition, it is valuable in the manufacture of medicines, cosmetics, and nutraceuticals. Taking advantage of the fact that FA is a nutraceutical additive, in the last decade several research groups throughout the world have been evaluating this phenolic compound with the aim of improving animal production (Ma et al., 2020; Macías-Cruz et al., 2018; Valadez-García et al., 2021; Wang et al., 2021).

3.1.4. Pharmacokinetics and bioavailability

The biological effectiveness of FA depends on its bioaccessibility from the food matrix and how it is absorbed, metabolized, and transported to the host's target tissues, i.e., its pharmacokinetics (Phan et al., 2020). As the majority of the plant-based polyphenols, the FA is poorly absorbed in the gastrointestinal tract (GIT) due to its esterified form in the cell wall (Adam et al., 2002). Consequently, supplementation of livestock with free FA or its derivatives is necessary to ensure its bioavailability and biological effectiveness (Cao et al., 2015).

3.1.4.1. Non-rumiants

Studies of FA pharmacokinetics in non-ruminants are limited to murine models. Ferulic acid in its free form is more bioavailable after ingested than FA as a component of the food matrix (Sova & Saso, 2020). The esterase enzymes action in the stomach is not efficient in releasing FA bound to the food matrix, and in consequence, only a small part of the total ingested FA is absorbed in the upper gut (Mancuso & Santangelo, 2014). The metabolism of absorbed FA takes place mainly in liver where the hydroxyl group is conjugated by glucuronidation and sulfation reactions (Kumar & Goel, 2019). After metabolism, albumin transports small or undetectable concentrations of conjugated FA through the bloodstream toward target tissues to exert its biological effects, and finally the metabolized FA via urine is excreted (Adam et al., 2002). On the other hand, non-released FA in stomach continues its passage to the large intestine, where the cecal microbiota transforms it into 3- (3-m-hydroxyphenyl) propionic acid for a higher hepatic β-oxidation. It is noteworthy that there is unreleased FA that is excreted directly in feces (de Paiva et al., 2013).

In contrast to FA from the food matrix, the free FA supplemented to animals is more bio-accessible and bioavailable because its absorption occurs in small intestine across monocarboxylic transporters (Sova & Saso, 2020). It is estimated that around 56% of free FA ingested crosses the intestinal barrier and reaches the liver through the portal system for metabolism (Adam et al., 2002). However, only 50% of this

metabolized FA is bioavailable to tissues and the remaining 6% is excreted in feces through biliary activity. The circulating blood concentration of this phenol reaches its peak within 30 min (Mancuso & Santangelo, 2014) and more than 90% of its excretion through urine occurs in the first 6 h post-ingestion (Kishida & Matsumoto, 2019).

3.1.4.2. Ruminants

In ruminants as in monogastric animals, FA from the feed matrix is less bio-accessible and bioavailable than in its free form. Forages and cereals used to feed ruminants are natural sources of FA (Table 1), but very little of this compound escapes from ruminal enzymatic activity (Soberon, Cherney, & Cherney, 2012). Once cell wall's breakdown occurs by the action of cellulolytic ruminal bacteria, microbial enzymes immediately transform most of the released FA into 3-phenylpropionic by hydrogenation-dihydroxylation reactions (Chesson et al., 1999). This 3-phenylpropionic is absorbed and metabolized in liver to benzoic acid, and finally excreted in urine as hippuric acid (Peña-Torres et al., 2019). The FA that escapes from microbial action may also be absorbed and conjugated in liver; however, its concentration in plasma and urine is almost undetectable (Soberon, Cherney, Liu, Ross, & Cherney, 2012).

On the contrary, the free FA offered through the diet to lactating cows had a rapid absorption after ingestion with maximum concentration in plasma and urine at 15 min and 2.7 h, respectively, but returning to basal concentrations at 5.5 h in plasma and 14 h in urine (Soberon, Cherney, Liu, et al., 2012). Similarly, Soberon, Cherney, and Cherney (2012) reported in free FA-fed sheep a reduction in circulating FA concentration within the first 5 h post-ingestion, being the urine the main route of excretion. Overall, these findings suggest that free FA is well absorbed and rapidly bioavailable in monogastric and ruminant animals but has a short time of availability. Therefore, future studies should establish both optimal dosage and supplementation frequency of FA to ensure prolonged action; in addition, researchers should consider differences among species, breeds, and physiological state.

3.1.5. Mechanisms of action in livestock

Supplemental FA improves livestock productivity by exerting multiple mechanisms of action. The first mechanisms involve its action as cytoprotective product (Mancuso & Santangelo, 2014) and adrenergic agonist (González-Ríos et al., 2016), although the latter is a very controversial issue. More recently, some studies suggest that it can also act as an antimicrobial agent (Ma et al., 2020; Shi et al., 2016), as well as intervene in muscle and gonadal activity by regulating gene expression (Chodkowska, Ciecierska, Majchrzak, Ostaszewski, & Sadkowski, 2018) and intracellular signaling pathways (Kuppusamy et al., 2019). Information on farm animals continues to be scarce, so more studies should be carried out to elucidate the different paths that this phenolic compound employs to induce biological effects.

3.1.5.1. Cytoprotective mechanisms

The FA acts as a bifunctional antioxidant in the presence of oxidative stress since it can directly eliminate free radicals and regulate the cellular antioxidant enzyme activity (Zhao & Moghadasian, 2008). The first function is associated with the chemical structure of this phenol as its phenolic hydroxyl group donates one hydrogen atom to free radicals for the formation of stabilized phenoxy radicals (Frankel, 2012, pp. 209–258). The second function is attributed to the fact that FA upregulates the expression of antioxidant enzymes (i.e., catalase, glutathione peroxidase, and superoxide dismutase) by activating the nuclear factor erythroid 2-related factor 2/antioxidant responsive element pathway (Nrf2/ARE; Mancuso & Santangelo, 2014). In this way, FA decreases the overproduction of reactive oxygen species (ROS) and increases antioxidant defense, leading to less oxidative damage of biomolecules (Ghosh, Basak, Dutta, Chowdhury, & Sil, 2017).

Other cytoprotective mechanisms exerted by FA include the upregulation of heat shock protein (HSP) expression and the avoidance of activation of apoptotic pathways (de Oliveira Silva & Batista, 2017). *In vitro* and *in vivo* studies have shown that FA increases the HSP32 and HSP70 expression (Ghosh et al., 2017; Hussein,

Abbas, Abulseoud, & El-Hussainy, 2017; Ma, Hong, Wang, Liang, et al., 2011; Shi et al., 2016; Song et al., 2014), proteins that decrease free radicals production (HSP32; Ma, Hong, Wang, Liang, et al., 2011) and prevent protein oxidation and catabolism (HSP70; Hussein et al., 2017). The anti-apoptotic action of FA is attributed to the activation of the Nrf2/ARE pathway (Song et al., 2016), the upregulation of anti-apoptotic gene expression (Chodkowska et al., 2018), or the direct binding of FA to cytochrome C to keep it stable (Yang et al., 2007).

Thus, by exercising the aforementioned cytoprotective actions, FA protects cells' structural and functional integrity (Hussein et al., 2017). In this sense, several studies carried out with laboratory and/or farm animals report that FA mitigates oxidative stress effects in enterocytes (He et al, 2016, 2018), hepatocytes (Song et al., 2014; Yu et al., 2018), β-cells in the pancreas (Ramar et al., 2012; Roy, Metya, Rahaman, Sannigrahi, & Ahmed, 2014; Salazar-López et al., 2017; Wang et al., 2015), cardiac cells (Song et al., 2014), muscle fibers (Li et al., 2015; Valadez-García et al., 2021), neurons (Hussein et al., 2017), lymphocytes (Ma, Hong, Wang, Liang, et al., 2011), erythrocytes (Ma, Hong, Wang, Tan, et al., 2011), Leydig cells (Hasanein, Fazeli, Parviz, & Roghani, 2018), gonads (Salma, Abdel, Karam, & El Hameed, 2019), and embryonic cells (Tanihara et al., 2018). Therefore, FA could improve physiological, metabolic, and immunological processes in animals with oxidative stress associated with stressors such as diseases, thermal stress, mobilization, others.

3.1.5.2. Adrenergic mechanisms

Free FA supplementation has been recommended as a natural alternative to the use of β-adrenergic agonists (β-AA) due to its possible β-adrenergic mechanisms (Valenzuela-Grijalva, Pinelli-Saavedra, Muhlia-Almazan, Domínguez-Díaz, & González-Ríos, 2017). Due to its similarity in chemical structure to epinephrine and norepinephrine, studies carried out in cattle and pigs suggest that this phenol can bind to β2 adrenergic receptors and exert the same biological responses as a synthetic β-AA (González-Ríos et al., 2013; Peña-Torres et al., 2019). Thus, FA may

stimulate the release of growth hormone (GH) and prolactin (Gorewit, 1983) at level of adenohypophysis and promote an anabolic action on muscle fibers (Herrera et al., 2011; Peña-Torres et al., 2021). So far, this is only a hypothesis and more research is required to confirm it. In nature, there are many similar-looking molecules but with totally different biological actions.

Valenzuela-Grijalva et al. (2017) mentioned that FA could inhibit the enzyme catechol-O-methyltransferase, which degrades epinephrine and norepinephrine. So, FA can increase serum catecholamine concentrations and, in consequence, their biological effects (Yalcin & Bayraktar, 2010). However, the lack of molecular evidence to support these mechanisms of action in farm animals, together with results in rats suggesting an antagonistic effect of FA on β1 and β2 receptors (Wu et al., 1998), leading to the implementation of additional studies on the possible activity of FA as β-AA.

3.1.5.3. Antimicrobial mechanisms

In vitro (Gong et al., 2019) and *in vivo* (Wang et al., 2019 ab) assays evidenced that this phenol modulates intestinal and ruminal bacterial populations and may be helpful to treat pathogenic microorganisms (Borges, Ferreira, Saavedra, & Simoes, 2013). According to Gong et al. (2019), FA in free form or bound to oligosaccharides stimulates the population growth of the enteric beneficial family *Bifidobacteriaceae* by acting as a fermentation substrate. Because of this change in the microbiota, FA also decreases the bacterial family *Enterobacteriaceae* population, microorganisms associated with amino acid degradation and GIT diseases. So, FA may promote better GIT health and higher microbial protein synthesis, as was recently proposed in lambs (Wang et al., 2019 ab). However, additional studies will be required to understand the complex interactions between FA and GIT microbiota, as well as implications in farm animals' health and productivity.

On the other hand, FA can be a natural alternative in treating common bacterial and viral diseases of economic importance in livestock. Studies with bacteria cultures (Borges et al, 2012, 2013; Saavedra et al., 2012) have shown that FA has an

antimicrobial effect on strains of *Escherichia coli, Pseudomonas aeruginosa, Listeria monocytogenes*, and *Staphylococcus aureus* that cause neonatal colibacillosis, urogenital infections, meningitis, and mastitis in farm animals (Smith, 2010). So, by altering the surface physicochemical properties and the cytoplasmic membrane integrity of these bacteria, this phenol compound causes cytoplasm hyperacidification, producing irreversible structural changes and cell death (Borges et al., 2013). Porcine parvovirus, a primary cause of sows' reproductive failure, is another disease that can be treated with FA (Smith, 2010). Ma et al. (2020) showed in a culture of porcine kidney cells that FA markedly prevented the ROS overproduction, inflammation, and apoptosis caused by the porcine parvovirus suppressing the Nuclear Factor-κB inflammasome axis and Toll-Like Receptor 4.

3.1.5.4. Mechanisms associated to differentiation of muscle fibers

The type of muscle fibers that animals develop in the prenatal stage largely defines the muscle development capacity and, consequently, the meat quality (Du, Wang, Xing, Yang & Zhu, 2015). Using mouse myoblasts of the C2C12 line, *in vitro* studies have shown that FA is involved in the differentiation and proliferation process of myoblasts (Chen et al., 2019; Kuppusamy et al., 2019). Kuppusamy et al. (2019) stated that FA stimulates the differentiation of C2C12 cells by regulating the expression of bone morphogenetic proteins, as well as activation of the Protein kinase B pathway (PKB or Akt) and extracellular signal-regulated kinases (ERK). Moreover, Chen et al. (2019) observed that FA triggers a preferential differentiation in muscle toward slowly oxidizing muscle fibers (type I) that are positively correlated with insulin sensitivity and improved meat quality. The mechanism involved in this function was the activation of the signaling pathway sirtuin 1 - adenosine monophosphate-activated protein kinase (Sirt1/AMPK).

3.1.5.5. Molecular mechanisms associated to muscle hypertrophy

Beside its effect similar to β-AA, FA could promote muscle hypertrophy in fattening animals due to its ability to regulate signaling pathways and myogenic gene

expression. Supplemental FA increases the slow-twitch fiber proportion in the *Longissimus thoracic* muscle (LTM) of weaned piglets due to the Sirt1/AMPK/PGC-1α pathway activation and improved mitochondrial function (Wang et al., 2021). In addition, FA activates the phosphatidylinositol 3 kinase/protein B kinase (PI3K/PKB or Akt) pathway in a similar way to the insulin-like growth factor I (IGF-I), which is reflected in higher muscle fiber diameter (Kuppusamy et al., 2019; Yeh, Hsu, Yang, Hsu, & Liu, 2014). At the level of myogenic gene expression, supplemental FA increased the transcription of myogenic regulatory factors (i.e., MyoD and myogenin) in zebrafish, obtaining better morphometric characteristics for skeletal muscle and higher body weight (Wen & Ushio, 2017). In horse satellite cells, it was reported that gamma oryzanol (compound rich in ferulate) stimulated higher cell proliferation and synthesis of sarcomeric proteins by regulating the expression of different genes associated with metabolic (*scd*), growth (*elavl1* and *Igf1r*), antioxidant (*nf2r2*), and anti-apoptotic (*Igf2*) activities (Chodkowska et al., 2018). However, these findings are still limited, so it is necessary to carry out more *in vivo* studies using production animals to verify the efficacy of FA, not only on transcription but also on the translation and expression of sarcomeric proteins, and consequently, on muscle hypertrophy.

3.1.6. Effects on animal metabolism

The FA has been shown to modulate animal metabolism mainly due to its cytoprotective capacity. In rats with high oxidative stress, FA improved insulin synthesis in pancreatic β cells due to its antioxidant and anti-inflammatory properties (Ramar et al., 2012; Roy et al., 2014; Salazar-López et al., 2017; Song et al., 2014; Wang et al., 2015). Similarly, Macías-Cruz et al. (2018) reported changes in the glucose-insulin system for pre-pubertal ewes fed free FA, particularly a reduction in serum glucose concentrations associated with high insulin synthesis. Meanwhile, FA-supplemented heifers had high GH production (Gorewit, 1983), which in turn could have stimulated a higher production of hepatic IGF-I (Chodkowska et al., 2018). It is noteworthy that feeding ruminants with FA does not affect serum triiodothyronine or

thyroxine concentrations under thermoneutral conditions (Gorewit, 1983; Macías-Cruz et al., 2018), but does in a hot environment. In fact, heat-stressed hair ewe lambs receiving supplemental FA had lower serum thyroxine concentration and oxidative stress index without altering serum triiodothyronine concentrations compared to control group (Valadez-García, 2019). The authors associated this finding with FA beneficial action on aerobic metabolism by an increased antioxidant defense, improved mitochondrial function, and higher thyroxine deiodination. If further studies confirm these mechanisms, the dietary supplementation of free FA could become a strategy to mitigate heat stress in small ruminants.

According to the aforementioned findings, it can be inferred that FA affects metabolic routes of the major nutrients, and consequently, favors both animal reproduction and growth (Figure 2). Concerning carbohydrate metabolism, free FA has demonstrated to stimulate cellular glucose uptake while maintaining euglycemia in sheep subjected to different environmental conditions (Macías-Cruz et al., 2018; Valadez-García, 2019; Wang et al., 2019 ab), as well as in hyperglycemic mice (de Oliveira Silva & Batista, 2017; Ramar et al., 2012; Roy et al., 2014). Perhaps, this adjustment in glucose metabolism due to FA is the result of increased circulating insulin concentration and the translocation of glucotransporters (GLUT4) towards the cell membrane (Kumar & Goel, 2019; Naowaboot et al., 2018), which in turn favors energy metabolism in tissues such as skeletal muscle (Chen et al., 2019; Chodkowska et al., 2018). Notably, this is a key response for animal reproduction and growth because glucose is the main energy source used by gonads and muscles.

The FA also could have anti-hyperlipidemic effects in obese farm animals as it decreases the biosynthesis of fatty acids, triglycerides, and cholesterol esters according to studies carried out with mouse C2C12 myoblasts exposed to hydrogen peroxide (Chodkowska et al., 2018) and rats fed a high-fat diet (Melo et al., 2017; Salazar-López et al., 2017). Using high fat diet-induced obese mice, Naowaboot et al. (2018) observed that dietary FA reduces lipid synthesis and stimulates lipolysis to counteract dyslipidemia by exercing an anti-insulin resistance effect. In contrast, no change was observed in serum triglycerides or cholesterol concentrations when fattening lambs received free FA supplementation (Macías-Cruz et al., 2014;

Valadez-García, 2019; Wang, Wang, et al., 2019), while FA-fed pigs (Li et al., 2015) and steers (González-Ríos et al., 2016) showed decreased meat lipid peroxidation rates. These findings suggest that FA modulates lipid metabolism only in presence of dyslipidemia. Overall, FA seems to act as a modulator of energy metabolism in animals with carbohydrate and lipid metabolic disorders. Concerning protein metabolism, the information available to date is limited to sheep under different climatic conditions. While this phenol does not affect serum concentrations of total protein and urea in hair ewe lambs experiencing heat stress or thermoneutral conditions (Macías-Cruz et al, 2014, 2018; Valadez-García et al., 2019), in cold stressed-male lambs it caused an increase in serum total protein concentration (Wang, Wang, et al., 2019). In lambs fed feruloyl oligosaccharides, an increase in serum total protein concentrations has also been evident (Wang, Meng, et al., 2019). Both studies explained that FA increases total protein in blood because improves microbial protein synthesis and/or enzymatic antioxidant activity preventing protein oxidation (Wang et al., 2019 ab). In consequence, FA might stimulate protein synthesis and reducing its catabolism (cytoprotective effect) in order to improve protein metabolism, at least in ruminants. This beneficial effect of FA on protein metabolism requires further study to accurately understand the mechanism of action in ruminants and other production animals.

3.1.7. Ferulic acid in animal production

3.1.7.1. Effects on meat production

The meat industry demands new technologies to produce healthy animals with high average daily gain (ADG), feed efficiency, and muscle mass deposition without provoking detrimental effects on meat quality. On the contrary, a meat with improved organoleptic properties, such as appearance, flavor and tenderness, and extended shelf life is desirable. In this regard, feeding feedlot animals with FA is a current nutritional technology that produces *ante*- and *postmortem* benefits in ruminants and monogastric animals (Table 2). Although, the beneficial effects of this phenol on meat production have not been entirely consistent throughout published studies, which has

been related to differences in factors such as specie, breed, sex, physiological state, oxidative status, dosage, and supplementation period (González-Ríos et al., 2016; Peña-Torres et al., 2019; Soberon, Cherney, & Cherney, 2012; Wang, Wang, et al., 2019). The main results reported for each species are described below.

Cattle

Most studies have reported no change for feedlot performance in FA-fed cattle (Flores-Campos et al., 2015; González-Ríos et al., 2013, 2016). Although, Peña-Torres et al. (2021) observed an increase in final BW and ADG, as well as a trend to increase feed efficiency without altering dry matter intake (DMI) due to free FA supplementation in beef heifers exposed to high environmental temperatures; these beneficial effects were more evident with increasing doses of FA (0, 250 and 500 mg kg^{-1} feed). In carcass characteristics, this phenol compound has been shown to improve carcass yield without affecting any other trait in steers fed 240 ppm of FA d^{-1} for 30 or 60 d (González-Ríos et al., 2013), as well as carcass weight and yield, and LTM area in heifers fed 250 mg of FA kg^{-1} feed but not with a dose of 500 mg kg^{-1} feed (Peña-Torres et al., 2021). All those studies indicate that FA acted as growth promoter similar to β2-AA to trigger a greater muscle mass deposition, and consequently, improved growth performance and carcass weight in beef cattle. As mentioned above, there is no sufficient evidence in the literature indicating that FA functions as β-AA, so other mechanisms of action could explain those beneficial effects; perhaps its antioxidant action is responsible given that the growing beef cattle experiences high metabolic rate and oxidative stress (Celi, 2011). Also, its antimicrobial mechanism of action in the modulation of ruminal fermentation could be considered.

Moreover, the dietary inclusion of free FA does not seem to affect physicochemical and sensory attributes of beef (González-Ríos et al., 2013, 2016; Peña-Torres et al., 2021). In fact, ultimate pH, color parameters, shear force, water holding capacity, cooking loss, intramuscular fat, and sensory traits (i.e., appearance, flavor, juiciness, and tenderness) were maintained within normal values in FA-

supplemented cattle (Peña-Torres et al., 2021). Satisfactorily, as a result of the antioxidant activity, FA decreases malondialdehyde and metmyoglobin concentrations but also increases the amount of polyunsaturated fatty acids (PUFAs) in meat (González-Ríos et al., 2016). From a biological point of view, the increase in PUFAs is favorable for the cellular and metabolic functions during the animal's growth, and consumer health (Sioen et al., 2017). Overall, FA contributes to the reduction of meat damage and the increase of its shelf life because it minimizes lipid and protein oxidation. In addition, this phenol helps to produce healthier meat for human consumption by modifying the lipid profile.

Sheep

The beneficial effects of FA supplementation on sheep meat production are controversial and possibly depend on the presence of high oxidative stress (Valadez-García et al., 2021; Wang et al., 2019 ab). Thus, there was no effect of dietary supplementation of free FA on growth performance, and carcass traits in Dorset x Finn (Soberon, Cherney, & Cherney, 2012) and Dorper x Pelibuey (Macías-Cruz et al., 2014) lambs finished under a thermoneutral environment. These results were associated with adequate pro-oxidant: antioxidant balance of the animals, and this prevented a cytoprotective action by feeding FA. On the contrary, FA-fed lambs that developed high oxidative stress due to temperatures below zero (Wang, Wang, et al., 2019) or higher than 35 °C (Valadez-García et al., 2021) had higher ADG and feed efficiency than control lambs by increasing antioxidant enzymatic activity and decreasing lipid and protein oxidation. In agreement with this finding, Wang, Meng, et al. (2019) reported similar results with feruloyl oligosaccharides in a dose-dependent manner when lambs were exposed to moderate heat stress. Peña et al. (2018) also observed an increase in the cross-sectional area of oxidative fibers without altering color parameters and shear force due to FA in sheep. Similarly, in heat-stressed ewe lambs fed FA, Valadez-García et al. (2021) reported better yields in some wholesale cuts where oxidative fibers predominated, with no change in LTM meat quality. Overall, these findings show that FA improves feedlot performance only when lambs

exhibit oxidative stress, which may be associated with a better antioxidant status and development of type I muscle fibers.

Pigs

Supplemental FA improves pig feedlot performance and some carcass characteristics, although the mechanism of action leading to these beneficial effects is unclear. In finished Landrace x Yorkshire pigs, supplementation of 15–25 ppm of FA kg^{-1} feed increased ADG, feed efficiency, final BW, and LTM area while decreasing fat thickness (González-Noriega, 2016; Herrera et al., 2011). As in cattle, the authors attributed these responses to a possible β-AA action of FA given that the antioxidant capacity of pigs was not affected. On the contrary, another study reported higher antioxidant capacity in the liver and LTM tissue without changes in back fat, lean percentage, and LTM area for FA-fed finishing pigs (100 ppm kg^{-1} feed; Li et al., 2015). Weaned pigs also did not respond to FA supplementation, as their feedlot performance did not change (Wang et al., 2021).

Results published so far suggest that the impact of FA on meat physicochemical characteristics and sensorial analysis depends on the dose administered, so that high doses are those that enhance these attributes of pork (Li et al., 2015). While the supplementation of 25 ppm of FA kg^{-1} feed promoted lipid peroxidation (González-Noriega, 2016), the feeding with 100 ppm of FA kg^{-1} feed decreased lipid oxidation in LTM (Li et al., 2015). Thus, high lipid peroxidation in meat caused a reduction in shelf life and a negative consumer perception regarding appearance and flavor (González-Noriega, 2016). On the contrary, low lipid oxidation had beneficial effects in pork, mainly improving tenderness and having a better red color (Li et al., 2015). As already indicated for other species, further studies are required to elucidate both mechanism of action and supplementation dose.

3.1.7.2. Effects on reproduction

The cyclical follicular production of ROS is essential for correct gonadal function, as they are necessary to produce energy and induce the ovulatory process (Kala, Shaikh, & Nivsarkar, 2017). On the other hand, elevated follicular ROS synthesis leads to oxidative stress, autoimmune premature ovarian failure and infertility in females (Mbemya, Vieira, Canafistula, Pessoa, & Ribeiro, 2017). In consequence, the exogenous supply of antioxidant compounds is a beneficial strategy to improve oxidative state and reproductive performance. The FA could promote better reproductive activity in farm animals due to its antioxidant activity (Tanihara et al., 2018), metabolic effect (de Oliveira Silva & Batista, 2017) and affinity for estrogen receptors (Kiyama, 2019; Table 3).

In prepubertal hair ewes, the dietary addition of free FA stimulated the reproductive tract development, follicular growth, and ovulation during the natural anestrus season (Macías-Cruz et al., 2018). The authors concluded that FA shortens puberty age and accelerates sexual maturity in lambs born in autumn. Similar results were reported in mice fed an extract rich in FA and in their offspring; additionally, higher estrogens and progesterone production was also observed in that study, with no change in luteinizing hormone and follicle stimulating hormone concentrations (Moshfegh et al., 2016). Heifers fed FA also show no change in the secretory activity of adenohypophysis gonadotropic cells (Gorewit, 1983). Therefore, these overall results seem to indicate that the reproductive benefits of this phytochemical are associated with a direct action at the ovary level. On the other hand, under *in vitro* conditions, gametes can experience cell damage from increased ROS production when exposed to atmospheric oxygen and a medium without antioxidant defense (Frankel, 2012, pp. 209–258). *In vitro* studies with prepubertal sow oocytes show that FA favors oocyte maturation and fertilization, and embryonic development due to its antioxidant function, specifically activating the Nrf2/ARE pathway (Lee & Hyun, 2017; Tanihara et al., 2018).

In addition to its antioxidant effect, FA modulates the ovarian endocrine function in the following ways: 1) its high affinity to estrogen receptors (Kiyama,

2019), 2) its pro-insulin action regulating the insulin-glucose system (de Oliveira Silva & Batista, 2017; Macías-Cruz et al., 2018), and 3) its ability to stimulate GH (Gorewit, 1983) and IGF-I (Chodkowska et al., 2018) release. The joint action of these mechanisms promotes a favorable metabolic environment in the ovaries to improve folliculogenesis and steroidogenesis, positively impacting follicular and luteal size, synthesis of steroidal hormone, and oocyte quality and maturation (Macías-Cruz et al., 2018; Moshfegh et al., 2016). High follicular and luteal endocrine activity due to FA helps the proper functioning of the hypothalamic-pituitary-gonadal axis (Tetaping et al., 2017).

In males, some benefits have also been reported due to FA. Rams with scrotal heat stress have reduced ROS levels and increased sperm motility without altering serum testosterone concentrations when fed a compound rich in FA (Escobar et al., 2019). In studies conducted in mice with testicular damage (Gawish et al., 2016; Hasanein et al., 2018) or diabetes (Roy et al., 2014), dietary FA reactivated endocrine and exocrine function of the testes. The cryopreservation of equine semen has also been favored with the addition of FA in the medium because it maintains mitochondrial, acrosomal, and plasma membrane stability (Affonso et al., 2017).

3.1.8. Restrictions

In contrast to the aforementioned benefits, improper use of FA can also have negative effects. Different studies have shown that high-dose supplementation in lambs (>2000 mg of FA kg^{-1} feed) or prolonged use in cattle (60 d) decreases nutrient digestibility (Wang, Wang, et al., 2019) or exerts pro-oxidant activity (González-Ríos et al., 2016), respectively. The first has been associated with the antibacterial action exerted by phenolic compounds on cellulolytic bacteria such as *Ruminococcus albus* and *R. flavefaciens* (Vasta et al., 2019). So, by reducing the availability of nutrients, productive benefits in feedlot and carcass may not be attained (Flores-Campos et al., 2015; González-Ríos et al., 2016; Macías-Cruz et al., 2014; Peña-Torres et al., 2021; Soberon, Cherney, & Cherney, 2012). On the other hand, the excessive accumulation of this phenol in tissues causes an increase in the iron reduction capacity and,

consequently, oxidative damage (Maurya & Devasagayam, 2010). Some studies have shown FA pro-oxidant activity in muscle, affecting negatively both quality and shelf life of the meat (González-Noriega, 2016; González-Ríos et al., 2016). Therefore, research is required to establish the specific doses for each species to avoid adverse effects from the use of FA.

3.1.9. Future prospects of ferulic acid in meat production

Based on mechanisms of action, and productive and reproductive effects, new possible applications of FA in the meat production chain could be suggested, but all must be previously validated. At first, supplemental FA could increase availability of animals for fattening, and its growth potential. In this sense, FA may be a viable option to ensure conception by enhancing natural and assisted reproduction programs. According to results in hair sheep and mice, FA stimulates sexual maturation (Macías-Cruz et al., 2018; Moshfegh et al., 2016) and improves gonads exocrine and endocrine function (Hasanein et al., 2018). If FA exerts these actions in breeds that present natural seasonal anestrus or in any farm animal species, it would be a promising natural alternative to induce early puberty and stimulate ovarian activity instead of synthetic hormones. In assisted reproduction, current information shows that FA is useful in artificial insemination and *in vitro* fertilization of sow oocytes due to its cytoprotective mechanisms (Affonso et al., 2017; Lee & Hyun, 2017; Tanihara et al., 2018); however, this needs to be tested on different species. During pregnancy, FA supplementation may be a strategy to improve fetal programming of muscle and gonads, and this could have long-term beneficial effects on the postnatal growth and development of the offspring. In murine models, FA stimulates differentiation of myoblasts to oxidative muscle fibers (Chen et al., 2019) and increases the number of follicles and corpus luteum in offspring (Moshfegh et al., 2016).

Feeding with FA may modulate the farm animals' growth during the fattening under adverse conditions. In ruminants, it has an antioxidant action that increases feed efficiency and weight gain in presence of oxidative stress associated with

thermal stress (Wang et al., 2019 ab; Valadez-García et al., 2021). Considering the current problem of global warming, this is a finding of particular interest since the supplementation of this natural antioxidant in animals exposed to extreme environmental temperatures may be a strategy to guarantee meat production in the context of climate change.

On the other hand, there is concern about the increasing antimicrobial resistance in livestock and that such resistance may be transmitted to humans; so, an alternative to the use of antibiotics in farm animals should be found (Clifford et al., 2018). Studies on bacterial cultures show that FA may modulate GIT microbiota (Gong et al., 2019) and has bactericidal action on some of the main zoonotic bacteria that cause several diseases in farm animals (Borges et al., 2013). Therefore, its activity as an eubiotic agent (Marquardt & Li, 2018) and *in vivo* therapeutic potential should be tested. Another possible antimicrobial application of this phenol may be its use as a preservative for meat since it inhibits bacterial biofilm formation in surfaces (Borges, Saavedra, & Simoes, 2012).

Finally, given that FA counteracts dyslipidemia (Salazar-López et al., 2017) and improves insulin sensitivity in muscle (Chodkowska et al., 2018), it can be an alternative to treat obesity in farm animals and insulin resistance in offspring born from dams subjected to nutritional restriction during the pregnancy. Underfed dams during pregnancy is a common issue in livestock systems with negative implications for offspring's postnatal metabolism and growth (Du, Wang, Fu, Yang, & Zhu, 2015). The main adverse effects are decreased myogenesis during the embryonic stage and lower muscle development, higher fat deposition, and peripheral insulin resistance in postnatal life (Khanal & Nielsen, 2017). The excessive accumulation of adipose tissue causes detrimental effects on meat quality in young animals (Corazzin, Bianco, Bovolenta, & Piasentier, 2019, pp. 119–165) and reproductive failure in adults (Khanal & Nielsen, 2017).

3.1.10. Conclusions

According to current information, FA can increase animal protein production by improving the productive and reproductive performance of farm animals. However, information remains scarce, leading to open an extensive field of research on the application of this phytochemical. Environmental conditions, species, oxidative state of the animal, bioavailability, mechanisms of action, and dosage of the product, are factors that should be considered in future research. Together, the information available to date and subsequent studies will allow the establishment of management strategies that make this natural compound a promising option to guarantee food safety without harming animal welfare and human health.

3.1.11. References

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3.1.12. Tables and figures

Table 1. Ferulic acid concentration in main ingredients used in animal nutrition.

Ingredient	Concentration (mg/g)	Reference
Alfalfa hay	1.5 - 2.6	Soberon et al., 2012a
Corn stover	5.3	Cao et al., 2015
Corn silage	5.8	Cao et al., 2015
Oat bran	0.33	Boz, 2015
Rye bran	2.8	Zhao & Moghadasian, 2008
Wheat bran	13.5 - 14.5	Zhao & Moghadasian, 2008
Corn grain	2.6 – 34	Bento-Silva et al., 2018
Oat grain	0.25 - 0.35	Boz, 2015
Wheat grain	13 – 14	de Paiva et al., 2013

Table 2. Effects of ferulic acid (FA) or derivates on feedlot performance, carcass characteristics and meat quality in ruminants and non-ruminants.

Animals	Dose/Period	Feedlot performance	Carcass traits	Meat quality (muscle *Longissimus thoracis)*	Reference
Heifers 3/4 *Bos Taurus*	0, 250 or 500 mg of FA kg^{-1} feed during 30 d	↑ Final BW and ADG, but DMI and feed efficiency unaffected	↑ HCW, CCW, carcass dressing, and MLT area, but fat thickness and marbling unaffected	Color, pH value, WBSF, cooking loss, WHC and sensory traits unaffected	Peña-Torres et al., 2021
Crossbred steers 3/4 *Bos Taurus*	6 mg of FA kg^{-1} BW during 30 (FA30) or 60 (FA60) d	Final BW unaffected	-	Physicochemical and sensory traits unaffected. FA30: delayed lipid peroxidation FA60: ↑ ∑ PUFAS	González-Ríos et al., 2016
Heifers and steers *Bos Taurus*	7 ppm of FA kg^{-1} BW during 56 d	ADG, DMI and feed efficiency unaffected	-	-	Flores-Campos et al., 2015
Crossbred steers 3/4 *Bos Taurus*	240 ppm of FA/d during 30 or 60 d	Final BW unaffected	HCW, CCW, fat thickness, and MLT area unaffected	physicochemical and sensory traits unaffected	González-Ríos et al., 2013

Dorset x Finn lambs	3, 6, and 9 g of FA/d during 5 d	↑ Feed intake and ADG unaffected with 3 and 6 g	-	-	Soberon et al., 2012a
Dorper x Pelibuey ewe lambs	300 mg of FA/d during 34 d	DMI, ADG, and feed efficiency unaffected	↑ Leg yield, without affecting other wholesale yields	-	Macías-Cruz et al., 2014
Male hair lambs	300 and 600 mg/d	-	-	↑ Area and diameter of oxidative fibers Unaffected color and WBSF	Peña et al., 2018
Dorper x Han cold-stressed lambs	80, 400, and 2000 mg of FA kg^{-1} feed during 30 d	↑ ADG and feed efficiency only with 80 mg. DMI and BW unaffected	-	-	Wang et al., 2019a
Dorper x Han heat-stressed lambs	50, 100, 200, and 400 mg of FOs kg^{-1} feed	↑ ADG and feed efficiency, but DMI and BW unaffected	-	-	Wang et al., 2019b
Katahdin x Dorper heat-stressed ewe lambs	250 mg of FA kg^{-1} feed during 40 d	↑ ADG and feed efficiency when Te > 35°C, without affecting final BW	↑ Forequarter wholesale cut yields ↓ Hindquarter wholesale	pH, color, and WBSF unaffected	Valadez-García et al., 2021

			cut yields		
Weaned piglets DLY	0.05 and 0.45% of FA inclusion in the diet	Final BW, ADG, DMI, and feed efficiency unaffected	-	↑ proportion oxidative-glycolytic muscle fibers and improved mitochondrial function	Wang et al., 2021
Landrace x Yorkshire pigs	25 ppm of FA kg^{-1} feed during 27 d	↑ ADG and final BW, but DMI and feed efficiency unaffected	↑ MLT area ↓ Fat thickness	↑ MDA ↓ Redness, flavor intensity, and WBSF	González-Noriega, 2016
Finishing pigs DLY	15 ppm of FA kg^{-1} feed	↑ ADG ↓ Feed conversion	↓ Fat thickness		Herrera et al., 2011
Barrows DLY	100 mg of FA kg^{-1} feed during 28 d	-	Lean percentage, MLT area, and fat thickness unaffected	↓ MDA and WBSF, but color and ultimate pH unaffected	Li et al., 2015

BW= body weight; ADG= average daily gain; DMI= dry matter intake; HCW= hot carcass weight; CCW= cold carcass weight; MLT= muscle *Longissimus thoracic;* WBSF= Warner-Bratzler shear force; WHC= water holding capacity; PUFAS= polyunsaturated fatty acids; n6= omega-6 fatty acids; MDA= malondialdehyde; FOs= feruloyl oligosaccharides; Te= ambient temperature; DLY= terminal breeding Duroc x Landrace x Yorkshire.

Table 3. Effect of ferulic acid (FA) or derivates on animal reproduction.

Animal/Cells	Dose	Response	Reference
Prepubertal hair ewes	300 mg of FA	↑ Peso del tracto reproductivo ↑ Masa y actividad ovárica ↓ Concentración sérica de glucosa	Macías-Cruz et al., 2018
Holstein heifers	100 and 500 mg of FA	↑ GH FA did not affect LH concentration	Gorewit, 1983
Female Balb / C mice	100 and 200 mg of date palm pollen rich in FA	↑ Size and ovarian activity of mothers and their offspring ↑ E_2 and P_4 ↑ Embryonic development	Moshfegh et al., 2016
Sow oocytes	10 µM of FA	↑ *In vitro* maturation, fertilization and blastocyst formation rate.	Lee & Hyun, 2017
Sow oocytes during *in vitro* maturation	5 µM, 10 µM, and 20 µM of FA	↑ GSH (5 µM) ↑ Blastocyst formation (10 µM) ↓ Intracellular ROS (20 µM)	Tanihara et al., 2018
Lambs with scrotal heat stress	33 mg of γ-oryzanol kg^{-1} metabolic weight	↓ ROS in testicles ↑ Sperm motility FA did not affect MDA, amount of parenchyma, or plasma testosterone concentration	Escobar et al., 2019
Mice with lead poisoning	50 mg of FA kg^{-1} BW	↓ MDA and ↑ GSH and TAC ↑ Number of germ and somatic cells in testis	Hasanein et al., 2018

Rats exposed to gamma radiation	50 mg of FA kg $^{-1}$ BW	↑ Testosterone and sperm quality ↓ MDA and ↑ catalase activity ↑ Testis size and testosterone concentration ↓ Sperm abnormalities	Gawish et al., 2016
Rats with induced diabetes	50 mg of FA kg $^{-1}$ BW	↑ Testis weight, testosterone concentration and sperm quality	Roy et al., 2014
Thawed equine semen	165 µM of FA at a sperm concentration of 25x106 cells/mL	↑ Integrity of plasma and acrosomal membrane and↑ mitochondrial potential	Affonso et al., 2017

GH = growth hormone; E2 = estrogens; P4 = progesterone; GSH = intracellular glutathione; ROS = reactive oxygen species; MDA = malondialdehyde; TAC = total antioxidant capacity.

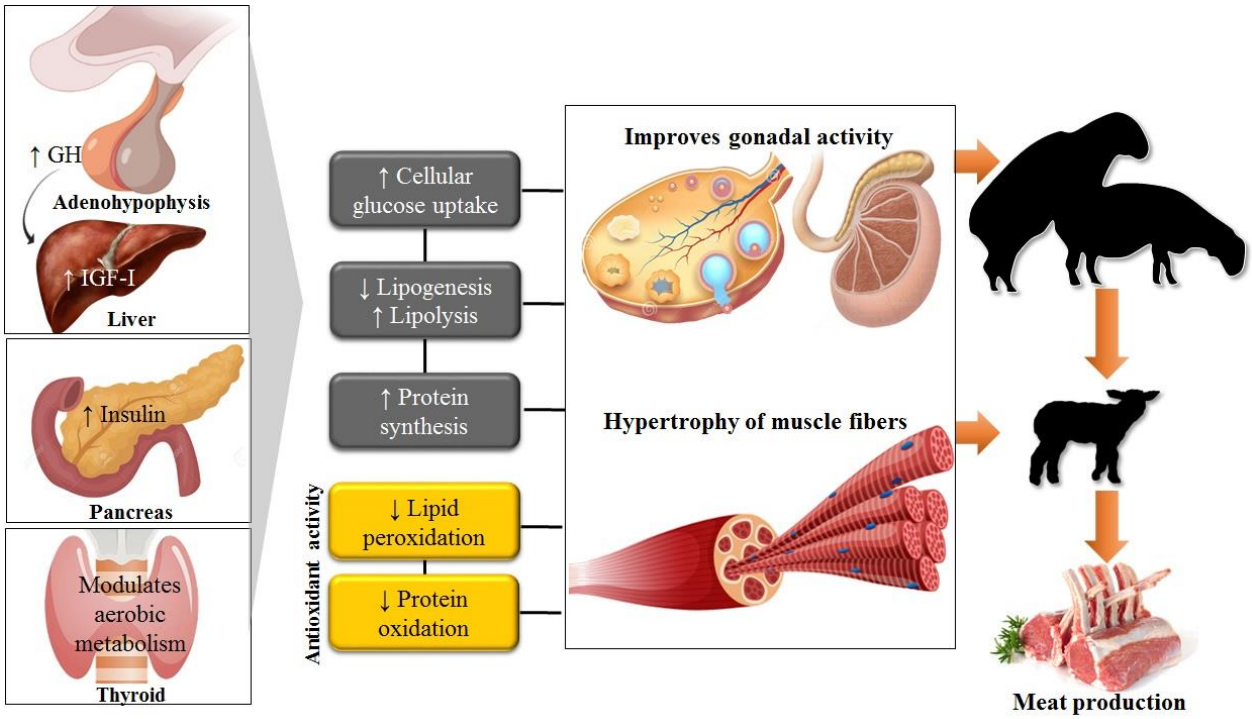

Figure 2. Effects of ferulic acid in animal metabolism (endocrine and cellular level) and implications in gonads and skeletal muscle function. GH = growth hormone; IGF-I = insulin-like growth factor type I.

3.2. Environmental, physiological, metabolic and growth factors defining the oxidative stress presence in hair breed lambs exposed to outdoor heat stress

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3.2.1. Abstract

Oxidative stress is an important cause of impaired productivity and welfare in heat-stressed hair lambs; however, it is still unclear that factors in these sheep breeds contribute to an oxidative imbalance in hot climates. This study aimed to establish the impact of environment, physiological responses, metabolism, and feedlot performance on serum oxidative stress biomarkers of hair lambs experiencing heat stress (HS). A total of 66 observations of physiological, metabolic, growth, and oxidative stress variables were taken from twenty-two Dorper × Katahdin ewe lambs (initial body weight= 23.5 ± 2.8 kg) finished during the summer in an arid region. Also, ambient temperature [Te], relative humidity [RH], and temperature-humidity index [THI]) were recorded during the feedlot period (40 d). Pearson's correlation and principal component analysis showed a positive association among oxidative stress biomarkers with average and minimum climatic conditions, maximum RH, morning rectal temperature, serum triglyceride and insulin concentrations, and feed efficiency, but negative association with maximum Te and THI, morning and afternoon respiratory rate (RR), serum total protein, and feed intake. According to stepwise regression, the variation of advanced oxidation protein products was explained by a negative and positive contribution of morning RR (partial R^2_{adj}= 0.45) and serum insulin (partial R^2_{adj}= 0.06), respectively; while mean malondialdehyde variation was explained by a negative contribution of maximum Te (R^2_{adj}= 0.43), and total oxidant capacity variation by a negative contribution of maximum Te (partial R^2_{adj}= 0.73) and positive of feed intake (partial R^2_{adj}= 0.03). In addition, the variation in total antioxidant capacity was explained by a negative contribution of maximum THI (R^2_{adj}= 0.52), and in oxidative stress index by positive contributions of maximum RH (partial R^2_{adj}= 0.13) and average daily gain (partial R^2_{adj}= 0.04). Overall, climatic conditions, morning respiratory rate and, to a lesser extent, productive performance are the factors regulating the oxidative stress presence in heat-stressed hair ewe lambs under a feedlot system.

Keywords: Hair sheep, Hot climates, Oxidative status, Thermoregulation adjustments, Energy metabolism, Growth.

3.2.2. Introduction

Hair breed sheep maintain relatively constant their core temperature as they are homeothermic animals; however, if the ambient temperature is higher than 30°C, these sheep increase their body heat load and experience heat stress (HS; Vicente-Pérez et al., 2020; Nicolás-López et al., 2021a). At the cellular level, HS in sheep causes oxidative stress characterized by an overproduction of reactive oxygen species (ROS) and insufficient antioxidant defense leading to impaired sheep's productivity and welfare (Belhadj et al., 2016; Chauhan et al., 2021). Recently, in heat-stressed hair ewe lambs from the Katahdin x Dorper genotype, it was shown that the oxidative stress levels depend on HS severity, being more harmful ambient temperatures above 35°C (Valadez-García et al., 2021). However, so far, the factors contributing to increased oxidative stress in hair sheep exposed to HS have not been determined.

According to previous reports in wool breed sheep, high oxidative stress is not only due to climatic environmental conditions but also to acclimatization adjustments under HS (Nicolás-López et al., 2021b; Akbarian et al., 2016; Chauhan et al., 2016). Belhadj et al. (2019) stated in wool cross breeds that there is a strong positive correlation of temperature-humidity index (THI) with oxidative stress index (OSI) and protein oxidation, as well as between serum malondialdehyde (MDA) and respiratory rate (RR). Chauhan et al. (2016) also reported in Merino x Poll Dorset lambs that the increase of respiratory evaporation causes high hydrogen peroxide (H_2O_2) levels in exhaled breath and may be an important source of oxidative stress. Furthermore, heat-stressed hair sheep have high redistribution of blood flow toward peripheral tissues to dissipate body heat load by skin radiation (Macías-Cruz et al., 2018); however, this vascular adjustment leads to hypoxia in internal organs, triggering extra production of free radicals (Belhadj et al., 2016). Moreover, ROS production during HS is directly related to energy and protein metabolism (Chauhan et al., 2021). Heat-

stressed lambs activate endocrine and metabolic mechanisms that, although they decrease endogenous heat production and guarantee energy availability (Al-Dawood, 2017; Nicolas-López et al., 2021a), also increase ROS production through accelerated aerobic and anaerobic pathways (Akbarian et al., 2016). In fact, the growth rate in sheep is positively associated with oxidative stress level because faster-growing lambs have accelerated metabolism and ROS production (Nussey et al., 2009).

Hair sheep are widely distributed meat breeds in warm regions and are preferred by farmers because they tolerate high temperatures well and are rustic with low reproductive seasonal (McManus et al., 2020; Vicente-Pérez et al., 2020). Thus, mutton production is constant throughout the year, which results beneficial for the sheep meat industry. However, as in all sheep breeds exposed to HS, oxidative stress is a latent problem that can partially compromise welfare and productive efficiency (Nicolas-López et al., 2021a). So, it is important to understand all biological mechanisms associated with impaired oxidative balance during HS, which, in turn, could help establish oxidative stress mitigation strategies. According to the background, it was hypothesized that the oxidative stress level exhibited by heat-stressed hair lambs depends on climatic conditions, physiological and metabolic acclimatization adjustments, and growth performance. Therefore, the objective was to establish the impact of climatic variables, physiological responses, metabolism, and feedlot performance on serum oxidative stress biomarkers of hair lambs exposed to outdoor HS conditions.

3.2.3. Materials and methods

3.1.3.1. Study site

The study was carried out during the summer season (August 10 to September 19, 2018) in the Sheep Experimental Unit of the Institute of Agricultural Sciences, Autonomous University of Baja California. The Institute is located in the desert region of Mexicali Valley (32° 24′N and 115° 22′W), where an arid and dry climate prevails

with low rainfall (85 mm/year), and extreme temperatures in summer (>40 ◦C) and winter (<0 ◦C) (INEGI, 2017).

3.2.3.2. Animals and management

All lambs' procedures were conducted within the guidelines established in Mexican Official Standard (Technical specifications for the production, care, and use of laboratory animals; NOM-062-ZOO-1999), as well as in the Federation Animal Science Society (FASS, 2010). Additionally, the Animal Care Committee of the University approved and supervised all experimental procedures. The study was carried out using data of 22 Dorper × Katahdin ewe lambs with initial body weight (BW) of 23.5 ± 2.8 kg and 4 months old. All sheep females were finished under feedlot system in individual pens for 55 d (15 d of adaptation period and 40 d of experimental phase), and received similar housing and feeding management. Individual pens (1 x 1.5 m) were provided of dirt floor, cyclonic mesh walls, galvanized sheet shade (2.5 m high), and two buckets, one for water and the other for *ad libitum* access to diet. The basal diet was formulated to meet nutritional requirements for finishing lambs (2.8 Mcal of metabolizable energy/kg dry matter [DM], and 16% crude protein; NRC, 2007) and was offered at 0600 and 1800 h. Dietary ingredients by kilogram of mixed feed were 100 g alfalfa hay, 150 g wheat straw, 620 g ground wheat grain, 110 g soybean meal, 5 g mineral/vitamin premix, 5 g limestone, 5 g dicalcium phosphate, and 5 g common salt.

3.2.3.3. Data collection

All data were collected across the 40-d trial period. Daily climatic conditions were measured with a thermohydrometer device (Thermotracker, Higro, Culiacán, Sinaloa, Mexico), which was placed in the middle of the study area and programmed to record temperature (Te) and relative humidity (RH) every 20 min. Data of Te and RH were used to estimate the THI with the formula proposed by Marai et al. (2007): THI = Te – [(0.31 – (0.31 * [RH/100])) * (Te – 14.4)]. For all climatic variables, daily

maximum and minimum average values, as well as overall daily average values, were calculated. Only climatic data of one week before each sampling day was considered.

All measurements of physiological and metabolic variables, as well as of oxidative stress biomarkers were carried out on experimental days 1, 20, and 40, obtaining 66 observations. Data of physiological response included morning (0500 h) and afternoon (1700 h) respiratory rate (RR) and rectal temperature (RT). First, RR was quantified by counting the number of intercostal movements during 30 s and expressed as breaths per minute (bpm); then, RT was measured with a digital thermometer (Delta Track, Pleasanton, CA, USA).

After sampling physiological variables and before morning feeding, blood samples from the jugular vein were collected in tubes without anticoagulant (10 mL), and then centrifuged at 3500×g for 15 min at 10 °C to separate serum and store it by duplicate in 2-ml vials at −20 °C until its use to determine analyte concentrations. Data of metabolism included serum concentrations of metabolites (i.e., glucose, cholesterol, triglyceride, total protein, and urea nitrogen (BUN)) and metabolic hormones (i.e., triiodothyronine (T3), thyroxine (T4), cortisol, and insulin). While metabolite concentrations were determined with a blood auto-analyzer of liquid phase (EasyVet; KrontroLab, Morelia, Mich., México), hormones concentrations were conducted with a fully automated ELISA analyzer (Thunderbolt, Gold Standard Diagnostics, CA, USA) using commercial kits (Monobind Inc., Lake Forest, CA, USA). The intra- and inter-assay coefficients of variation were 5.4 and 6.7 % for T3, 1.6 and 6.1 % for T4, 6.4 and 7.0 % for cortisol, and 4.9 and 5.6 % for insulin. Oxidative stress measurements in serum were concentrations of advanced oxidation protein products (AOPP), malondialdehyde (MDA), total oxidant capacity (TOC), and total antioxidant capacity (TAC). In addition, oxidative stress index (OSI) was also calculated as TOC/TAC ratio (Karaagac et al., 2011). The oxidative stress quantifications were carried out by spectrophotometry (Bio-Tek Instruments, Inc., Winooski, VT, USA) following the method of chloramine-T (Witko-Sarsat et al., 1996), *N*-methyl-2-phenyl-indole (Witko-Sarsat et al., 1998), o-dianisidine (3,3′ -dimethoxybenzidine) (Erel, 2005), and ABTS radical cation (Erel, 2004) for serum determination of AOPP, MDA, TOC, and TAC, respectively.

Feedlot performance data included initial and final body weight, average daily gain (ADG), feed intake, and feed efficiency. Ewe lambs were individually weighed before morning feeding at the beginning and end of the study, and this information was used to calculate ADG. The daily amount of feed offered and refused per animal was also recorded to calculate feed intake and feed efficiency.

3.2.3.4. Statistical analysis

All statistical procedures were developed using the Statistical Analysis System 9.4 (SAS Inst. Inc., Cary, NC, USA). Previous to statistical analysis, the Shapiro-Wilk normality test was applied to all study variables using PROC UNIVARIATE. Then, a descriptive statistical analysis was performed for all variables using PROC MEANS. Pearson correlation among oxidative stress biomarkers, climatic conditions, physiological variables, serum metabolite and hormone concentrations, and feedlot traits were determined with PROC CORR. Correlation coefficients (r) values were declared significant at $P \leq 0.05$ and classified as low ($r < 0.35$), moderate ($0.36 < r < 0.67$) or strong ($r > 0.68$) (Taylor, 1990). In addition, a principal component (PC) analysis was carried out based on all the parameters measured using PROC PRINCOMP. Only the first two PC that had eigenvalues ≥ 1 (Jolliffe, 1973) were plotted. Finally, multiple linear regression (MLR) analysis was performed using PROC REG, where oxidative stress biomarkers were dependent variables while climatic, physiological and metabolic variables, as well as feedlot traits were predictor variables. The STEPWISE regression and Mallow's Cp criteria were used to select the variables included in the models. In each MLR model developed, residual analysis was applied to identify and delete observations outside critical values of two or more indicators (i.e., RS Student, Leverage, DFITTS, COV RATIO, and DFBETAS). Then, coefficient of determination (R^2), adjusted coefficient of determination (R^2adj), root means square error (RMSE), the variance inflation factor (VIF), as well as tests of Durbin-Watson (DW) and lack of fit (LF) were considered to evaluate the models' goodness of fit. The individual contribution of the variables selected in final models

was reported according to partial R^2 and R^2adj, which, in turn, were calculated from the sum of type III squares.

3.2.4. Results

Descriptive statistics for study variables are shown in Table 4 and 5. Mean values ± standard deviation of Te, RH, and THI were 33.5 ± 0.8 °C, 52.5 ± 4.5 %, and 30.3 ± 1.0 units, respectively, the highest variation was observed in minimum RH (coefficient of variation (CV) 19.0 %). Regarding physiological response, in the morning, the ewe lambs had an average RR and RT of 105 ± 19 bpm and 39.7 ± 0.2 °C, respectively; in the afternoon, these values increased 65.2 and 0.5 units, respectively. Mean values of serum metabolites ranged from 6.5 ± 0.7 mg/dL (total protein) to 82.5 ± 7.2 mg/dL (glucose), the higher variation was observed for triglycerides (CV 49.2%) and the lowest for glucose (8.7%). For serum hormones concentrations, the CV for T4 was 22.5 %, T3 35.7 %, and insulin and cortisol > 54%. Average values of ADG, feed intake, and feed efficiency were 0.2 ± 0.1 kg, 1.1 ± 0.2 kg, and 0.2 ± 0.1 kg/kg, respectively, with a CV of 18.2% for feed intake and 50% for ADG and feed efficiency. A large variation was observed in oxidative stress biomarkers since CV ranged from 33.3% (OSI) to 66.7% (TAC).

Results of Pearson correlation coefficients (*r*) are shown in Table 6**.** In general, most oxidative stress biomarkers showed low to strong positive correlation ($P < 0.05$; $0.24 \leq r \leq 0.79$) with all average and minimum values of climatic variables, maximum RH, morning RT, triglycerides, insulin, and feed efficiency. However, negative associations ($P < 0.05$; $-0.21 \leq r \leq -0.85$) were observed among oxidative stress biomarkers with maximum Te and THI, morning and afternoon RR, total protein, and feed intake. Additionally, there is low positive correlation ($P < 0.05$; $r = 0.27$) between OSI and ADG, and low negative correlation ($P < 0.05$; $-0.24 \leq r \leq -0.30$) of TAC with urea and ADG.

The first two autovectors for the variables examined are in Figure 3. The total variance explained by PCs was 50%, of which 40.7 % was attributed to PC1 and 9.3 % to PC2. The PC1 was mainly loaded ($-0.27 \geq r \leq 0.28$) with all climatic variables,

TOC, morning RR, insulin, and feed intake, while PC2 was loaded (-0.38 ≥ *r* ≤ 0.44) with ADG, feed efficiency, morning and afternoon RT, OSI, and TAC. According to PC1, while there was a positive association among TOC, MDA, and AOPP with average and minimum Te and THI, RH values, and insulin, a contrary association was observed between these oxidative stress biomarkers with maximum Te and THI, morning RR, and feed intake. On the other hand, PC2 showed that heat-stressed ewe lambs with higher ADG and feed efficiency and lower RTs increased OSI and decreased TAC.

Results of MLR analysis among oxidative stress biomarkers and regressor variables are shown in Table 7 and 8. In general, models of oxidative stress biomarkers included maximum climatic conditions, morning RR, insulin, feed intake, and ADG. The partial contribution of these variables in each model is mentioned below. Fifty-one percent of the total variation observed in AOPP concentration was explained by a negative contribution of morning RR (partial R^2_{adj}= 0.45) and positive contribution of insulin (partial R^2_{adj} = 0.06). The maximum Te contributed negatively to variation of MDA (R^2_{adj} = 0.43) and TOC (partial R^2_{adj} = 0.73); additionally, the feed intake also had a lower positive contribution in TOC variation (partial R^2_{adj} = 0.03). While maximum THI negatively contributed to explain 52 % of TAC total variation (*P* < 0.01), both maximum RH (partial R^2_{adj} = 0.13) and ADG (partial R^2_{adj} = 0.04) positively contributed to explain only 17% (*P* < 0.001) of the total OSI variation.

3.2.5. Discussion

3.2.5.1. Heat stress responses

According to results of climatic conditions, our ewe lambs were exposed to extremely severe HS since the Te exceeded the upper limit of the hair sheep's thermoneutral zone (15-30 °C; Vicente-Pérez et al., 2020) and THI was higher than 25.6 units (Marai et al., 2007). As a result of this hot environmental conditions, the ewe lambs increased their body heat load, reaching RT values above the normal physiological range (i.e., 38.3 – 39.9 °C; Al-Dawood, 2017), followed by activation of thermoregulation mechanisms, impaired feedlot performance, and presence of

oxidative stress. In congruence with previous studies (Macías-Cruz et al., 2018; McManus et al., 2020; Nicolás-López et al., 2021), our heat-stressed hair lambs increased respiratory evaporation in an effort to dissipate their body heat load, and also made metabolic adjustments to decrease metabolic heat production, maintain anabolism, and avoid catabolism. In addition, the mean values obtained for feedlot traits were in agreement with those previously reported for hair breed lambs subject to outdoor HS (Macías-Cruz et al., 2013, 2020). Note that reference values established for oxidative stress biomarkers in hair sheep were not found in the literature; however, results of this study agreed with those reported in some studies conducted with hair lambs finished in hot environments (Wang et al., 2019; Valadez-García et al., 2021). In general terms, the average values of the study variables coincide with those reported for heat-stressed hair lambs in the study region.

3.2.5.2. Pearson's correlations and principal components analysis

The HS induces oxidative stress in hair sheep, impairing their productivity and welfare (Belhadj et al., 2019). This latter has been evidenced when heat-stressed lambs have lower oxidative damage and improved meat production because of antioxidant supplementation (Wang et al., 2019; Valadez-García et al., 2021). However, in hair sheep breeds subjected to HS, both pathways and molecular mechanisms involved in ROS overproduction and poor functioning of antioxidant systems are still unknown. In this sense, we hypothesized that the oxidative stress level exhibited by heat-stressed hair lambs depends on climatic conditions, physiological and metabolic acclimatization adjustments, and growth performance. Our results seem to support this hypothesis, since all climatic variables and some physiological and metabolic responses, as well as growth performance traits were relationships to oxidative stress biomarkers.

The higher correlations were observed between climatic conditions and oxidative stress measurements, which were confirmed by the PC analysis. Consistent with a previous report (Belhadj et al., 2019), our results also showed a positive association between serum oxidative stress biomarkers and average and minimum

values of Te and THI; however, negative correlations were observed in the current study when ewe lambs were exposed to maximum Te values. This interesting finding confirms the thermotolerance in these sheep breeds, and might be related to cellular adjustments for ensuring cell survival under extreme HS conditions (41-45 °C and 35-38 units of THI). In hot environment, increased accumulation of ROS in ruminant cells triggers the activation of two conserved cytoprotective responses: 1) expression of inducible heat shock proteins (HSPs), and 2) downregulation of the oxidative metabolism mediated by the hypoxia-inducible factor-1 (HIF-1; Baumgard and Rhoads, 2013; Archana et al., 2017). So, as a result of the chaperone action of HSPs and decreased mitochondrial ROS production, the cell counteracts oxidative stress followed by its survival while promoting acclimatization of the animal (Baumgard and Rhoads, 2012; Ely et al., 2014; Belhadj et al., 2016). In this sense, it has been shown that Pelibuey hair breed sheep are more thermotolerant to HS than Suffolk wool breed sheep because their cells produce high amount of HSP70 to survive the thermal insult (Romero et al., 2013). With regard to HIF-1 activation, there are no studies to date in heat-stressed sheep; however, there are evidences in rats (Sanders et al., 2009), pigs (Pearce et al., 2015), and cattle (Baumgard and Rhoads, 2013). Future research is needed to test HSP70 and HIF-1 importance in hair sheep subjected to different degrees of HS.

In the current study, hair ewe lambs showed lower levels of all oxidative stress biomarkers as morning and afternoon RR increased; in contrast, Belhadj et al. (2019) reported in heat-stressed wool breeds a strong positive correlation between MDA and RR. In fact, the authors proposed the high activity of the respiratory tract as a direct source of ROS in sheep under HS conditions. Note that respiratory evaporation is the main heat dissipation mechanism in sheep (Marai et al., 2007); therefore, the lower oxidative stress observed in our ewe lambs might be associated with the effectiveness of RR to restore normothermia in them (McManus et al., 2020; Nicolás-López et al., 2021). This latter was especially evident during the morning when they maintained their normothermia and RT had lower positive correlations with oxidative stress biomarkers. In addition, heat-stressed sheep have been shown to excrete high concentrations of H_2O_2 in exhaled breath condensate (Chauhan et al., 2016). So,

respiratory elimination of H_2O_2 could also explain the negative relationships between RR and serum oxidative stress biomarkers.

As expected, both correlation and PC analysis results showed that oxidative stress in heat-stressed hair ewe lambs is positively associated with energy metabolism and feedlot performance. These findings could be explained by an accelerated metabolism to meet high maintenance and growth energy requirements, which, in turn, promotes ROS overproduction (Nussey et al., 2009; Chauhan et al., 2021). Not surprisingly, the strongest and lowest correlation between oxidative stress and metabolic traits was observed between insulin and TOC and between triglycerides and MDA, respectively. In hot environment, adapted lambs change their post-absorptive metabolism creating a hyperinsulinemic state to ensure efficient partitioning of nutrients towards muscle while avoiding adipose tissue mobilization (Mahjoubi et al., 2014, 2015; Macías-Cruz et al., 2020; Nicolás-López et al., 2021a). Note that our ewe lambs had slightly higher insulin concentrations (0.90 ng/mL) than previously reported in other studies conducted on heat-stressed hair (0.60 ng/mL; Nicolás-López et al., 2021b) and wool (0.38 ng/mL; Mahjoubi et al., 2015) male lambs. This seems to explain, not only the direct positive relationship of serum insulin concentrations with oxidative stress biomarkers, but also the positive correlations of oxidative stress biomarkers with ADG and feed efficiency, as well as the negative correlations between oxidative stress biomarkers and serum total protein concentrations. Altogether, these associations suggest an increased muscle deposition modulated by insulin and, consequently, a high metabolism rate and oxidative stress (Nussey et al., 2009). On the other hand, lipid catabolism is an important source of ROS and MDA (Celi, 2011), so a strong and positive correlation is expected between concentrations of oxidative stress markers and metabolites associated with lipid metabolism; situation that was not observed in the current study as serum triglyceride concentrations had a low relationship with MDA and none with OSI. This is attributed to the hyperinsulinemic metabolic environment in ewe lambs that led to low lipolytic activity.

3.2.5.3. Multiple linear regression analysis

Based on correlation and PC analysis, the serum concentration of oxidative stress biomarkers is associated with at least one of the different climatic, physiological, metabolic, and feedlot performance traits. However, considering the MLR analysis results, only one or two of these variables can explain between 20 and 74% of the total variation of oxidative stress biomarkers. It should be mentioned that each regression equation complies with the assumptions of normality, linearity, and independence. This is supported by results of the LF, DW, and VIF tests, which showed absence of pure error ($P \geq 0.17$), independence between sampling days ($P \geq 0.10$; d= 1.66 to 2.14), and absence of collinearity (VIF < 10) between independence variables selected in the models. To our knowledge, there are no previous reports of explanatory or prediction models for oxidative stress biomarkers in heat-stressed hair or wool breed sheep. Thus, models are being proposed for the first-time to explain the variation of AOPP, MDA, TOC, TAC, and OSI from climatic, physiological, metabolic, and feedlot performance traits in hair sheep experiencing HS.

According to the AOPP model, the variation of protein oxidation depends on morning RR (R^2_{adj} partial= 0.37) and, to a lesser extent, of energy metabolism modulated by insulin (R^2_{adj} partial= 0.05). As discussed earlier, the lower AOPP concentration due to increased morning RR suggests the effectiveness of respiratory evaporation to restore normothermia and eliminate H_2O_2 in the exhaled breath condensate, which appears to be especially helpful at night. It is known that the HS severity in hair sheep depends on diurnal Te fluctuations. So, while our ewe lambs gained heat in the daylight hours, they dissipated excess body heat load through respiratory evaporation in dark hours of the day (Vicente-Pérez et al., 2020). This adaptive mechanism developed by hair sheep helps them not only to avoid dehydration (Nicolás-López et al., 2021ab; Vicente Pérez et al., 2020) but also to counteract oxidative damage. Regarding energy metabolism, despite there was a relationship of AOPP with triglycerides, total protein, insulin, feed intake, and feed efficiency, the final model developed for AOPP only included insulin. This was expected as lipid and protein metabolism as well as feedlot performance of heat-

stressed lambs are under insulin regulation (Baumgard and Rhoads, 2013; Mahjoubi et al., 2015).

Interestingly, final models indicated that the variation in MDA concentrations depends only on maximum Te values while the variation in TAC on maximum THI values. This situation was attributed to low correlations ($-0.36 \leq r \leq 0.32$) among dependent and independent variables, likewise elimination of multicollinearity effect among maximum Te and THI with the other predictor variables. In congruence with our correlation and PC analysis, MLR results revealed a decrease of serum MDA and TAC concentration for each unit increased in maximum Te ($R^2_{adj} = 0.27$) and THI ($R^2_{adj} = 0.52$), respectively. The cytoprotective action of HSP's and HIF-1 pathways are factors that might contribute to these responses (Baumgard and Rhoads, 2013; Romero et al., 2013) and the higher variation explained by maximum Te (R^2_{adj} partial= 0.72) in the TOC equation. Furthermore, an increase in serum TOC concentration also depends, to very low extent, on feed intake (R^2_{adj} partial= 0.02) due to the increased production of metabolic heat and ROS (Chauhan et al., 2021).

Finally, an increment of 13 % in OSI value was explained by maximum RH values ($P < 0.01$) and 6 % by ADG ($P = 0.04$). The variation attributed to the environmental RH supports the importance of an adequate vapor pressure gradient that allows heat dissipation through evaporative pathways (Collier et al., 2019). For its part, the higher protein and energy metabolism in our ewe lambs as their growth rate increased explains the ADG contribution (Nussey et al., 2009). Notably, predictor variables selected in the model explained low OSI variation ($R^2_{adj} = 0.17$) in comparison to the other equations. This latter was expected because the OSI biomarker provides an index of the general oxidative stress status (Celi, 2011); hence, it was mostly associated with TOC ($P < 0.0001$; $r = 0.58$) and TAC ($P < 0.05$; $r = -0.32$) than with those used independent variables ($P < 0.05$; $-0.28 \leq r \leq 0.38$).

3.2.6. Conclusions

The serum oxidative stress biomarkers of hair ewe lambs exposed to environmental HS were mainly defined by climatic conditions, morning RR and, to a

lesser extent, by serum insulin concentrations and feedlot performance traits (i.e., feed intake, ADG, and feed efficiency). Thus, the protein oxidation in hair ewe lambs fattened under outdoor HS is mainly associated to a decrease in their morning respiratory rate, while the body fat oxidation and overall oxidant capacity is associated to a decrease in maximum environmental temperatures. In addition, the total antioxidant capacity of these fattening animals is mostly favored by a reduction in the maximum THI values.

3.2.7. References

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3.2.8. Tables and figures

Table 4. Descriptive statistics for climatic conditions recorded during the experimental period.

Items	Mean	SD	Min	Max	CV (%)
Temperature (°C)					
Average	33.5	0.9	32.4	34.6	2.6
Minimum	25.3	2.4	22.6	28.4	9.5
Maximum	43.8	1.8	41.2	45.2	4.2
Relative humidity (%)					
Average	52.5	4.5	46.1	55.8	8.7
Minimum	23.9	4.5	17.7	28.2	19.0
Maximum	79.8	2.7	76.1	82.3	3.3
Temperature-humidity index (units)					
Average	30.3	1.0	29.0	31.5	3.4
Minimum	24.7	2.2	22.4	27.6	8.8
Maximum	36.9	1.1	35.3	38.0	3.1

SD standard deviation, *Min* minimum values, *Max* maximum values, and *CV* coefficient of variation.

Table 5. Descriptive statistics for physiological, metabolic, feedlot performance, and oxidative stress traits on hair lambs exposed to environmental heat stress.

Items	Mean	SD	Min	Max	CV (%)
Physiological (°C)					
Respiratory rate (bpm), 0600 h	105.0	19.0	60.0	136.0	18.1
Respiratory rate (bpm), 1800 h	170.2	17.0	138.0	212.0	10.0
Rectal temperature (°C), 0600 h	39.7	0.2	39.1	40.2	0.5
Rectal temperature (°C), 1800 h	40.2	0.4	39.3	41.0	1.0
Metabolism					
Glucose (mg/dL)	82.5	7.2	64.4	103.9	8.7
Cholesterol (mg/dL)	43.8	10.8	25.8	68.9	24.7
Triglycerides (mg/dL)	35.4	17.4	12.1	96.6	49.2
Urea (mg/dL)	41.9	6.0	21.5	50.4	14.3
Total protein (mg/dL)	6.5	0.7	4.8	8.3	10.8
Triiodothyronine (ng/mL)	1.4	0.5	0.9	4.6	35.7
Thyroxine (ng/mL)	8.0	1.8	4.7	13.3	22.5
Insulin (ng/mL)	0.9	0.5	0.2	2.2	55.5
Cortisol (µg/dL)	3.3	1.8	0.6	8.3	54.5
Feedlot performance					
Average daily gain (kg)	0.2	0.1	0	0.3	50.0
Feed intake (kg)	1.1	0.2	0.8	1.5	18.2
Feed eficciency (kg/kg)	0.2	0.1	0	0.4	50.0
Oxidative stress					
Advanced oxidation protein products (µmol/L)	6.9	2.4	3.7	18.4	34.8
Malondialdehyde (µmol/L)	1.5	0.6	0.8	3.9	40.0
Total oxidant capacity (µmol Eq H_2O_2/L)	6.3	3.4	1.9	14.6	54.0
Total antioxidant capacity (µmol Eq Trolox/L)	1.2	0.8	0.4	6.0	66.7
Oxidative stress index (arbitrary units)	0.6	0.2	0.1	1.0	33.3

SD standard deviation, *Min* minimum values, *Max* maximum values, and *CV* coefficient of variation.

Table 6. Pearson correlation coefficients (*r*) among oxidative stress biomarkers and climatic conditions, physiological, metabolic, and feedlot performance traits on hair lams exposed to environmental heat stress.

Items [a]	AOPP	MDA	TOC	TAC	OSI
Climatic conditions					
Temperature average	0.66***	0.44**	0.75***	0.47***	0.36**
Temperature minimum	0.66***	0.46***	0.78***	0.49***	0.35**
Temperature maximum	-0.60***	-0.53***	-0.85***	-0.59***	-0.28*
Relative humidity average	0.53***	0.20	0.41**	0.18	0.36**
Relative humidity mínimum	0.61***	0.32**	0.58**	0.32*	0.38**
Relative humidity maximum	0.61***	0.32*	0.58***	0.31	0.38**
THI average	0.65***	0.40**	0.69***	0.41**	0.37**
THI mínimum	0.65***	0.48***	0.79***	0.51***	0.35**
THI máximum	-0.52***	-0.54***	-0.82***	-0.61***	-0.21***
Physiological					
Respiratory rate, am	-0.62***	-0.36**	-0.55***	-0.29*	-0.28*
Respiratory rate, pm	-0.18	-0.24*	-0.48***	-0.34**	-0.12
Rectal temperature, am	0.15	0.29*	0.34**	0.32**	-0.01
Rectal temperature, pm	0.06	0.003	0.06	0.13	0.01
Metabolism					
Glucose	-0.006	-0.06	-0.12	-0.03	-0.10
Cholesterol	0.03	-0.06	-0.13	-0.10	-0.13
Triglycerides	0.33**	0.28*	0.43***	0.37**	0.15
Urea	-0.21	-0.14	-0.20	-0.24*	0.02
Total protein	-0.32**	-0.40***	-0.52***	-0.34**	-0.15
Triiodothyronine	0.17	-0.04	0.17	0.01	0.18
Thyroxine	-0.04	0.001	0.04	0.05	0.008
Cortisol	0.05	0.04	-0.14	-0.05	-0.17

Insulin	0.55***	0.54***	0.76***	0.38**	0.35*
Feedlot performance					
Average daily gain	0.006	-0.17	0.12	-0.30*	0.27*
Feed intake	-0.55***	-0.42***	-0.44***	-0.38**	-0.08
Feed eficciency	0.24*	0.002	0.33**	0.14	0.30*

AOPP advanced oxidation protein products, *MDA* malondialdehyde, *TOC* total oxidant capacity, *TAC* total antioxidant capacity, and *OSI* oxidative stress index, and *THI* temperature-humidity index. * $P < 0.05$, ** $P < 0.001$, *** $P < 0.0001$, and no asterisk indicates non-significant ($P > 0.05$) correlation between variables.

Table 7. Equations of multiple linear regression to evaluate association between oxidative stress biomarkers and climatic, physiological, metabolic, and feedlot performance traits on hair lambs exposed to environmental heat stress.

Equation	*n*	RMSE	R^2	R^2_{adj}	*P*	P < DW	P > DW	LF (*P*)
AOPP= 12.91 – 0.07 RRam + 1.54 Insulin	50	1.77	0.53	0.52	< 0.0001	0.14	0.86	0.18
MDA= 10.06 – 0.20 Tmax	64	0.42	0.44	0.43	< 0.0001	0.10	0.90	0.39
TOC= 81.40 – 1.82 Tmax + 4.38 FI	64	1.62	0.77	0.76	< 0.0001	0.32	0.68	0.87
TAC= 13.87 – 0.35 THImax	65	0.37	0.53	0.52	< 0.0001	0.11	0.89	0.83
OSI= – 2.04 + 0.03 RHmax + 0.91 ADG	66	0.21	0.20	0.17	< 0.001	0.68	0.32	0.20

AOPP advanced oxidation protein products, *MDA* malondialdehyde, *TOC* total oxidant capacity, *TAC* total antioxidant capacity, *OSI* oxidative stress index, *Tmax* maximum temperature, *THImax* maximum temperature-humidity index, *RHmax* maximum relative humidity, *RRam* morning respiratory rate, *FI* feed intake, *ADG* average daily gain, *RMSE* root means square error, R^2 coefficient of determination, R^2_{adj} adjusted coefficient of determination, *P < DW* Durbin Watson test for positive autocorrelation, *P > DW* Durbin Watson test for negative autocorrelation, and *LF* lack of fit test.

Table 8. Partial contributions of climatic, physiological, metabolic, and feedlot performance traits to the variations observed in oxidative stress biomarkers on hair lambs exposed to environmental heat stress.

	Estimator	SE	R^2 partial	R^2_{adj} partial	VIF	*P*
Advanced oxidation protein products						
Intercept	12.91	2.13	-	-	0	< 0.0001
RRam	-0.07	0.02	0.46	0.46	1.45	0.0001
Insulin	1.32	0.65	0.06	0.06	1.45	0.0100
Malondialdehyde						
Intercept	10.06	1.24	-	-	0	< 0.0001
Tmax	-0.20	0.03	0.44	0.43	1.00	< 0.0001
Total oxidant capacity						
Intercept	81.40	5.40	-	-	0	< 0.0001
Tmax	-1.82	0.14	0.74	0.73	1.63	< 0.0001
FI	3.95	1.74	0.03	0.03	1.63	0.009
Total antioxidant capacity						
Intercept	13.87	1.51	-	-	0	< 0.01
THImax	-0.35	0.04	0.53	0.52	1.00	< 0.01
Oxidative stress index						
Intercept	-2.04	0.79	-	-	0	0.01
RHmax	0.03	0.01	0.14	0.13	1.00	< 0.01
ADG	0.91	0.44	0.06	0.04	1.00	0.04

RRam morning respiratory rate, Tmax maximum temperature, FI feed intake, THImax maximum temperature-humidity index, RHmax: minimum relative humidity, ADG average daily gain, SE Standard error, R^2 coefficient of determination, R^2_{adj} adjusted coefficient of determination, and VIF variance inflation.

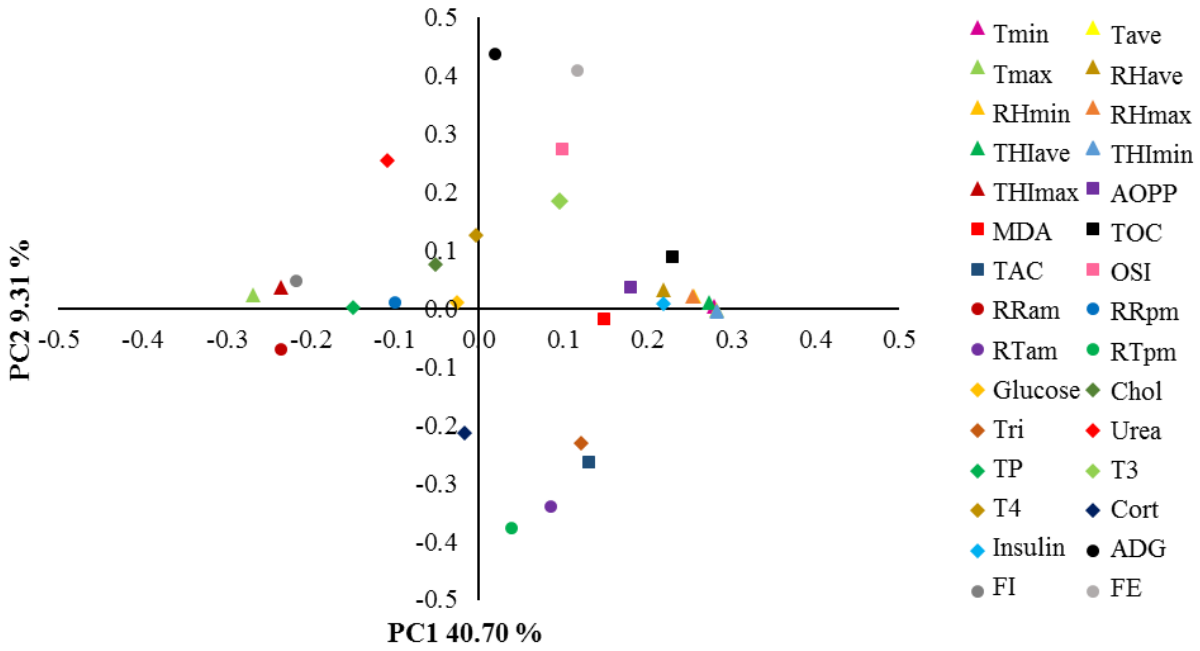

Figure 3. Principal components (PC) for climatic conditions, oxidative stress, physiological, metabolic, and feedlot performance traits on hair lambs exposed to environmental heat stress. *Tmin* minimum temperature, *Tave* average temperature, *Tmax* maximum temperature, *RHmin* minimum relative humidity, *RHave* average relative humidity, *RHmax* maximum relative humidity, *THImin* minimum temperature-humidity index, *THIave* average temperature-humidity index, *THImax* maximum temperature-humidity index, *AOPP* advanced oxidation protein products, *MDA* malondialdehyde, *TOC* total oxidant capacity, *TAC* total antioxidant capacity, *OSI* oxidative stress index, *RRam* morning respiratory rate, *RRpm* afternoon respiratory rate, *RTam* morning rectal temperature, *RTpm* afternoon rectal temperature, *Chol* cholesterol, *Tri* triglycerides, *TP* total protein, *T3* triiodothyronine, *T4* thyroxine, *Cort* cortisol, *ADG* average daily gain, *FI* feed intake, and *FE* feed efficiency.

3.3. Free ferulic acid supplementation of heat-stressed hair ewe lambs: Oxidative status, feedlot performance, carcass traits and meat quality

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3.3.1. Abstract

Twenty-two Katahdin × Dorper ewe lambs (average weight = 23.5 ± 2.8 kg) were individually housed during a 40-d feeding study and then slaughtered to evaluate effects of free ferulic acid (FA; 0 and 250 mg/kg of feed) on oxidative status, feedlot growth, carcass and non-carcass traits, wholesale cut yields and meat quality under heat stress conditions. Overall feeding FA decreased protein oxidation without affecting oxidative stress index, while growth rate and feed efficiency increased only in the hottest period (i.e., 28 to 45 °C). The FA supplementation increased kidney-pelvic-heart and mesenteric fat deposition, as well as yields of forequarter, shoulder, ribs, loin, and breast and flank, but decreased yields of hindquarter, neck, plain loin and leg. Carcass characteristics and meat quality were unaffected by FA. Overall, FA supplementation of heat-stressed hair ewe lambs enhanced feedlot performance under extreme heat stress and increased internal fat reserves, while changing muscle mass deposition, possibly because it prevented protein oxidation.

Keywords: Fattening lamb, Mutton tenderness, Natural antioxidants, Oxidative stress Phenolic compound, Warm climate.

3.3.2. Introduction

Hair sheep are widely distributed in arid, semi-arid and tropical regions, where their productivity is compromised during hot summers (Sejian et al., 2017). When hair sheep breeds are exposed to an ambient temperature > 30 °C, they begin to suffer heat stress (HS; Vicente Pérez et al., 2020), which causes the sheep to activate physiological, metabolic, endocrine, and cellular mechanisms to thermoregulate. Although such mechanisms are effective in restoring normothermia in hair sheep breeds, they also increase maintenance energy needs (Macías-Cruz et al., 2013, 2020) and cause high oxidative stress (Belhadj, Chniter, Najar, & Ghram, 2019). As a consequence, heat-stressed hair lambs decrease their average daily gain (ADG), feed efficiency, cold carcass weight (CCW) and loin yield, as well as produce slightly

tougher meat associated with its high ultimate pH and low water holding capacity (Macías-Cruz et al., 2013, 2020).

Use of natural antioxidants can be a useful strategy to mitigate HS effects on meat production of hair sheep. Some authors have stated that plant extracts with antioxidant actions enhance growth performance, carcass traits and meat quality in heat-stressed wool lambs. In a hot summer study, the naringin flavonoid increased ADG and feed efficiency in Awassi lambs (Alhidary & Abdelrahman, 2016), while the lycopene carotenoid improved hot carcass weight (HCW) in Bamei lambs (Jiang et al., 2015). Similarly, heat-stressed Ujumqin lambs fed chestnut tannins had enhanced growth performance, while lipid and myoglobin oxidation in skeletal muscle was prevented (Liu, Li, Mingbin, Zhao, & Xiong, 2016). However, there are no previous reports on use of any natural antioxidant under hyperthermia conditions in fattening hair lambs.

Ferulic acid (FA) is a phenolic compound that has received attention in the livestock sector because of its antioxidant properties. This phenolic compound scavenges free radicals and induces expression of antioxidant enzymes by activating the nuclear factor E2-related factor 2/antioxidant element response pathway (Nrf2/ARE; Ghosh, Basak, Dutta, Chowdhury, & Sil, 2017). Associated with these mechanisms, FA can improve physiological and metabolic processes, and therefore, animal growth (González-Ríos et al., 2016; Wang, Wang, et al., 2019). In thermoneutral conditions, FA decreased shear force of finishing pig meat the resultant longer storage stability (González-Ríos et al., 2016). In contrast, FA in sheep did not affect feedlot performance and carcass characteristics under optimal ambient temperatures (Macías-Cruz et al., 2014; Soberon, Cherney, & Cherney, 2012), whereas in cold stressed lambs (Wang, Wang, et al., 2019), it increased ADG and feed efficiency by enhancing oxidative status. This suggests that, in fattening lambs, FA has greater effects only in association with the presence of high oxidative stress. However, this has not been demonstrated in heat-stressed lambs of any breed.

This study was designed to test the hypothesis that FA enhances productive performance, carcass characteristics, wholesale cut yields and meat quality in heat-

stressed hair ewe lambs by improving oxidative status. Thus, the objective was to evaluate effects of dietary supplementation of free FA on oxidative status markers, feedlot performance, carcass and non-carcass traits, wholesale cut yields, and meat quality in heat-stressed ewe lambs.

3.3.3. Materials and methods

3.3.3.1. Study site

The study was carried out during summer (i.e., August and September) at the Sheep Experimental Unit and Meat Laboratory of the Instituto de Ciencias Agrícolas (ICA), Universidad Autónoma de Baja California (UABC). The ICA-UABC is located in the Mexicali Valley, Baja California, northwestern México (32° 24′ N and 115° 11′ W), where the climate is arid and dry, with extreme temperatures in summer (>40 °C) and winter (<0 °C). In this region, rainfall is low (85 mm/year) and occurs mainly during winter (INEGI, 2017).

3.3.3.2. Animals, management and treatments

All experimental procedures of management and slaughter of lambs were according to FASS guidelines (FASS, 2010) and Mexican Official Norms: NOM-062-ZOO-1999, Technical specifications for the production, care and use of laboratory animals; NOM-051-ZOO-1995, Humanitarian treatment in animal mobilization; and NOM-033-SAG/ZOO- 2014, Humanitarian slaughter of domestic and wild animals.

Twenty-two Katahdin × Dorper ewe lambs with initial body weight (BW) of 23.5 ± 2.8 kg and aged 4 months were used in a 55-d feeding study (15 d for adaptation and 40 d for feedlot evaluation). During the adaptation period, all lambs were adapted to individual pens and basal diet, with concomitant sanitary management of a single subcutaneous administration of 0.2 mg/kg BW of ivermectin (Iverfull; Aranda Laboratory, Mexico City, Mexico), and intramuscular administration of 250,000 IU of vitamin A, 37,500 IU of vitamin D and 25 mg of vitamin E (Vigantol ADE strong; Bayer Laboratory, Mexico City, Mexico). The individual pens had an area of 1.5 m^2, cyclonic

mesh walls, dirt floor, galvanized sheet metal shade (2.5 m height), and a bucket for diet and another for water. The basal diet was formulated to meet nutritional requirements for fattening lambs in the finishing phase (11.7 MJ metabolizable energy [ME]/kg dry matter [DM] and 16% crude protein [CP]) (NRC, 2007).

After the adaptation period, the initial BW of each lamb was recorded to create pairs of similar BW as a blocking factor. Ewe lambs of each pair were randomly assigned to one of the two dietary treatments (*n* = 11): basal diet with 0 (control) or 250 mg of FA/kg of feed. The FA dosage was determined according to a previous study (González-Ríos, Gil, & Berrondo, 2013), where a dosage of 250 mg/kg of diet was recommended for finishing cattle. To ensure optimal FA intake, all ewe lambs were weighed individually every 10 d to calculate daily feed intake (BW*0.04), and consequently expected daily FA intake. Therefore, the daily amount of FA fed per lamb was based on expected daily feed intake, which was 235, 258, 275, and 295 mg during days 1 to 10, 11 to 20, 21 to 30 and 31 to 40, respectively, of the feeding period. The FA was mixed with ground wheat grain to create the FA dose of 250 mg into 30 g of mixture, so that the mixture amount that contained the expected daily FA intake per lamb female was weighed and offered daily before the morning feeding. In the control group, 30 g of ground wheat grain was offered as placebo before the morning feeding. Treatments were offered during the 40-d feedlot evaluation period.

The diet was offered twice (0600 and 1800 h) and the water three times a day (0600, 1200 and 1800 h) to guarantee ad libitum access. Diet samples were collected weekly, dried in forced-air oven at 60 °C for 24 h, milled through a 2-mm screen (Wiley mill model 4; Thomas Scientific, Swedesboro, NJ, USA) and mixed to obtain two subsamples, which were used for chemical analyses (AOAC, 1990; Van Soest, Robertson, & Lewis, 1991). The ME was calculated according to NRC (1985). Ingredients and chemical composition of the diet are shown in Table 9. Health status of the lambs was monitored daily by direct visualization, and none showed signs of disease during the study.

3.3.3.3. Climatic conditions and physiological variables

Daily climatic conditions were measured with a thermohygrometer (Thermotracker, Higro, Culiacán, Sinaloa, Mexico) placed in the middle of the study area at a height similar to that of the lambs' heads and programmed to record temperature (Te) and relative humidity (RH) every 20 min. The temperature-humidity index (THI) was obtained using the formula (LPHSI, 1990) modified by Marai, El-Darawany, Fadiel, and Abdel-Hafez (2007): THI = Ta - [(0.31 - (0.31 * HR)) * (Ta - 14.4)]. In all climatic variables, daily average, maximum and minimum values were calculated for 10-d periods and overall. Additionally, averages per hour were estimated.

Rectal temperature (RT) and respiratory rate (RR) were measured at 0600 and 1800 h on days 1, 10, 20, 30 and 40 of the feeding periods. The RR was quantified by counting the number of intercostal movements by 30 s, multiplied by two to obtain the number of breaths per minute (bpm). The RT was obtained by inserting a digital thermometer (Delta Track, Pleasanton, CA, USA) rectally until the temperature remained constant for at least 30 s.

3.3.3.4. Serum oxidative status markers

On days 1, 20 and 40, the serum concentrations of malondialdehyde (MDA), advanced oxidation protein products (AOPP), total oxidant capacity (TOC), total antioxidant capacity (TAC) and oxidative stress index (OSI) were measured. Blood samples were collected at 0600 h (before the morning feeding) from the jugular vein into 6-mL vacutainer tubes, which were centrifuged at 3500 × g for 15 min at 10 °C. Serum was stored in duplicate in 2-mL vial at -20 °C until analysis. Oxidative markers were quantified with a microplate spectrophotometer (Bio-Tek Instruments, Inc., Winooski, VT, USA), according to the methodologies: *N*-methyl-2-phenyl-indole method for MDA (Witko-Sarsat et al., 1998), chloramine-T method for AOPP (Witko-Sarsat et al., 1996), o-dianisidine (3,3′ -dimethoxybenzidine) method for TOC (Erel, 2005), and ABTS radical cation method for TAC (Erel, 2004). The OSI was estimated using the TOC/TAC ratio (Karaagac, Tekin, Koruk, & Aksoy, 2011).

3.3.3.5. Feedlot performance

Individual BW was recorded every 10 d before the morning feeding. The amounts of feed and water offered and refused were recorded by lamb daily. From this data, ADG, total BW gain, DM intake, feed efficiency and daily water intake were calculated for 10-d periods (1 to 10, 11 to 20, 21 to 30 and 31 to 40 d) and for the overall period (1 to 40 d). Both initial and final BW were also considered.

3.3.3.6. Carcass characteristics and non-carcass components

Once the feedlot phase was completed, lambs were fasted for 12 h and then transported to the Meat Laboratory for slaughter by the exsanguination method described in the Official Mexican Standard NOM-033-SAG/ZOO-2014. All lambs were bled, skinned and eviscerated to measure individual HCW and weights of non-carcass components such as blood, skin, head, feet, full and empty gastrointestinal tract, heart, liver, spleen, kidneys, pelvic-renal-heart fat (KPH), and omental and mesenteric fat. Carcasses were chilled at 4 °C for 24 h to obtain CCW, conformation (scale from 1 = bad to 8 = excellent; Smith, Griffin, & Kenneth, 2001) and morphometric measurements as carcass length, thorax depth, leg length, and leg perimeter (Par´es-Casanova, 2013). Subsequently, carcasses were ribbed along the midline, and the right half was ribbed again between the 12th and 13th rib to facilitate measure of *Longissimus thoracis* (LT) muscle area (dot square grid of 64 mm^2) and fat thickness (vernier caliper). Hot and cold carcass yields were calculated expressing the HCW and CCW as a percentage of the empty BW (EBW = slaughter BW – [full – empty gastrointestinal tract]). The KPH fat weight was expressed as a percentage of the HCW, and the rest of the non-carcass component weights were expressed as percentages of the EBW.

3.3.3.7. Wholesale cut yields

The right half carcass was weighed and sectioned according to Avendaño-Reyes et al. (2011) into the cuts: forequarter, hindquarter, neck, loin, ribs, shoulder,

plain loin, leg, and breast and flank. The weight of each cut was expressed as a percentage of the half carcass weight to obtain yield.

3.3.3.8. Meat quality evaluation

The LT muscle was used to evaluate meat quality traits (i.e., pH, color and shear force). At 45 min and 24 h *postmortem*, a portable pH meter provided with a penetration electrode (Hanna Instruments, model HI 98140, Woonsocket, RI, USA) was used to measure pH in the carcass loins at the height of the 12th and 13th rib where the LT is located. The loin wholesale cut (loin of the 4th to 12th ribs) contained the LT muscle, so it was dissected after its weight was recorded. The LT muscle was vacuum packaged, aged (14 d at 4 °C) and finally unpacked for blooming. Five grams of muscle sample were separated within the first minute of blooming to determine storage pH, likewise a steak to measure shear force. The meat sample was liquefied with 25 mL of distilled water and the storage pH was measured directly in the mixture with a benchtop pH meter (Model HI-2210, Hanna Instruments Digital, Woonsocket, RI). For shear force, steaks were cooked until an internal temperature of 71 °C (electric skillet, Cook Master Oster, model 3222-3, Mississauga, ON, Canada; Meat thermometer Hanna, model HI-93551, Woonsocket, RI, USA and then cooled at 25 to 30 °C) to cut 1.27 cm cubes on each side. Cooked meat cubes were sheared in longitudinal orientation to the muscle fibers with a Warner-Bratzler shear force device (Salter 235, Manhattan, KS, USA). The meat color was measured after 30 min of blooming. A colorimeter (Model CR-400, Konica Minolta Sensing, Inc., Osaka, Japan; D65 illuminator and 10° observer) was collocated on the surface of the meat to record lightness (L*), redness (a*), yellowness (b*), color saturation index (Chroma, C*) and Hue angle (H*). All meat quality measurements were made in triplicate for each lamb.

3.3.3.9. Statistical analysis

All statistical analyses were developed using the SAS program (SAS Inst. Inc., Cary, NC, USA). Climatic variables were analyzed with PROC MEANS to obtain values of descriptive statistics. The Shapiro-Wilk normality test was applied to all

study variables using PROC UNIVARIATE. Data of ISO presented a non-normal distribution ($P > .05$), so they were transformed with the log function to obtain normality. Data of overall feedlot performance, carcass characteristics, non-carcass components, wholesale cut yields and meat quality were subjected to analysis of variance in a randomized complete block design (RCBD) using PROC MIXED. Physiological variables, feedlot performance by period and oxidative stress markers were also subjected to analysis of variance, but using a RCBD with repeated measures over time where the models included fixed effects of block, FA supplementation, time (sampling day or period) and the FA supplementation x time interaction. Different variance-covariance structures were verified to fit the model, and the compound symmetry structure showed the best fit according to criteria of lowest BIC and AIC values (Littell, Henry, & Ammerman, 1998). Treatment means were compared using LSMEANS/PDIFF to declare differences at $P \leq .05$ and trends at $0.05 < P \leq .10$. In the absence of interaction ($P > .05$), means by time were analyzed with orthogonal polynomials.

3.3.4. Results

3.3.4.1. Climatic conditions and physiological variables

Daily averages for Te, RH and THI were 33.41 ± 1.74 °C, 53.92 ± 8.07% and 30.37 ± 1.68 units, respectively. The hottest conditions occurred in the first 10 d (Te = 35.35 °C, RH = 55.74% and THI = 32.22 units) and were slightly lower during the last 30 d (Figure 4). The Te remained above 30 °C from 0800 to 2200 h and THI above 22.2 units during the 24 h (Figure 5), with average minimum and maximum values at 0600 (Te = 25.33 ± 3.07 °C and ITH = 24.57 ± 2.91 units) and at 1600 h (Te = 44.13 ± 2.44 °C and ITH = 37.36 ± 1.47 units). In the case of physiological variables, FA supplementation did not affect ($P \geq .30$) RR and RT in the morning or afternoon; however, the sampling day caused variation ($P < .01$) in them, since both variables had a quartic effect in the morning and a cubic effect in the afternoon as the feedlot days increased (Table 10).

3.3.4.2. Oxidative stress markers

The FA supplementation x sampling day interaction did not affect ($P \geq .18$) serum concentrations of any oxidative stress marker (Table 11). In general, supplemental FA tended ($P = .06$) to decrease serum AOPP concentration, without modifying ($P \geq .20$) serum levels of MDA, TOC, TAC and OSI. The MDA, TOC, and TAC decreased quadratically ($P < .01$), and AOPP and OSI decreased linearly ($P < .01$) with progression of the feeding period.

3.3.4.3. Feedlot performance

While FA supplementation did not alter ($P \geq .38$) overall feedlot performance (Table 12), the FA supplementation x period interaction affected ($P < .05$) productive variables, but not ($P \geq .15$) water intake (Figure 6). During the first 10 d, there were higher ($P \leq .01$) ADG, total BW gain and feed efficiency due to FA feeding, without affecting ($P = .45$) DM intake. Between days 11 and 20, FA supplementation increased ($P = .05$) DM intake with no change ($P \geq .15$) of ADG, total BW gain and feed efficiency. However, in d 21 to 40, feedlot performance was unaffected ($P \geq .22$) by FA.

3.3.4.4. Carcass and non-carcass traits, wholesale cut yields and meat quality

Feeding FA increased ($P \leq .03$) KPH and mesenteric fat deposition, and tended ($P = .07$) to decrease leg perimeter, without affecting ($P \geq .11$) any other carcass characteristics or fat deposition (i.e., HCW, CCW, carcass yields, conformation, MLT area, carcass length, thorax depth, leg length, fat thickness and omental fat; Table 13). However, FA supplementation increased ($P \leq .04$) yields of forequarter, shoulder, and breast and flank, as well as tending to increase loin ($P = .08$) and rib ($P = .10$) yields, but decreased ($P \leq .04$) yields of hindquarter, neck, plain loin and leg (Table 14). Non-carcass components (Table 15) and meat quality traits (Table 16) were unaffected ($P \geq .11$) by FA.

3.3.5. Discussion

3.3.5.1. Climatic conditions and physiological response

Ewe lambs were exposed to high environmental Te (33.4 °C), exceeding the upper limit of its thermoneutral zone (30 °C; Vicente- Pérez et al., 2020) and experiencing constant HS during the feedlot phase, which was extremely severe in terms of THI (THI ≥ 25.6 units; Marai et al., 2007). It is noticeable that overall environmental conditions were even hotter in the first 10 days of the study (Te = 35.3 °C and THI = 32.2 units) and then declined slightly the following 30 days (Te = 32.7 °C and THI = 29.7 units). As a result, the ewe lambs experienced hyperthermia most of the daytime because their evaporative heat losses were insufficient to dissipate accumulated heat load (RT = 40.2 °C and RR = 172 bpm). At dawn, there was slight thermal relief, since they had decreased their core temperature by 0.4 °C overmorning. That the free FA did not affect RT and RR in our ewe lambs is similar to results reported in heat-stressed wool sheep fed another natural antioxidant (Alhidary & Abdelrahman, 2016).

3.3.5.2. Oxidative stress

To our knowledge, this is the first study using free FA to improve the oxidative status in heat-stressed sheep. Inexplicably, results showed that this FA did not decrease the overall oxidative stress by increasing the TAC in hair ewe lambs suffering hyperthermia. Previous studies have reported better TAC and antioxidant enzyme activity in Dorper x Han lambs fed FA under cold stress (Wang, Wang, et al., 2019), as well as when they were fed feruloyl oligosaccharides (FA derivative) under moderate HS (Wang, Meng, et al., 2019). These beneficial effects occurred in a dose-dependent manner, with better responses at low dosages. Thus, we suggest that our oxidative state results may be associated with a long gap between FA feeding and sampling times because free FA is rapidly metabolized and excreted in ruminants about 4 to 5 h post-ingestion (Soberon et al., 2012), and blood samples were taken 24 h after the last FA ingestion. Future studies could be conducted to determine optimal dose and frequency of supplemental free FA for hair lambs fattened under HS

and, if FA is offered in a single daily dose, it is recommended to measure oxidative stress markers before 5 h post-ingestion.

Interestingly, the supplemental FA was particularly effective in reducing protein oxidation (AOPP), but not lipid peroxidation (MDA), which could have beneficial implications to maintenance of muscle mass deposition and growth rate despite a hot environment. As FA can prevent protein damage by stimulating heat shock protein (Hsp's 32 and 70) expression (Ghosh et al., 2017), it is likely that free FA reduced serum AOPP levels by increasing chaperone HSP action.

Our results partially support our hypothesis, that free FA supplementation would enhance feedlot performance, carcass characteristics, wholesale cut yields and meat quality in heat-stressed hair ewe lambs by improving oxidative status, as the FA-fed ewe lambs had lower protein oxidation, better feedlot performance in the first days and higher yield of some wholesale cuts. However, free FA failed to improve overall oxidative status, carcass traits and meat quality.

3.3.5.3. Feedlot performance

Feeding FA was effective in improving feedlot performance of heat-stressed hair ewe lambs in the first 10 d of the experimental period when conditions were hottest (i.e., Te > 35 °C) and the lambs had the highest OSI. This confirms the hypothesis raised in previous studies (Macías- Cruz et al., 2014; Wang, Wang, et al., 2019) which is that dietary supplementation of free FA enhances feedlot performance, but only in fattening lambs with high oxidative stress because of its antioxidant action. A similar growth response occurred in heat-stressed lambs fed feruloyl oligosaccharides (Wang, Meng, et al., 2019) while, in lambs with high oxidative stress caused by cold stress, feeding of free FA had positive effects on productivity (Wang, Wang, et al., 2019).

Some studies in murine model have reported that FA avoids HS-induced epithelial barrier dysfunction by activating the Nrf2/ARE pathway and Hsp32 expression (He et al., 2018), and that it prevents oxidative damage in pancreatic β-cells and improves insulin synthesis (Ghosh et al., 2017). In contrast, excessive

reactive oxygen species (ROS) production in heat-stressed ruminants can cause intestinal epithelial injuries, resulting in lower nutrient absorption and high penetration of pathogens and endotoxins (Sejian et al., 2017). Finally, as HS promotes hyperinsulinemia to increase cellular glucose availability, avoids mobilization of body reserves and reduces synthesis of non-esterified fatty acids; this latter compound promotes pancreatic β-cell apoptosis (Baumgard & Rhoads, 2013). Thus, another possible reason for positive impacts on productive performance in the hottest period of the feeding phase could be because FA supplementation improved intestinal health and function, and also the glucose-insulin system.

On the other hand, supplemental FA did not exert long-term beneficial effects (day 10 to 40) on productive performance, which could be associated with a change in its mechanisms of action when heat and oxidative stress began to decline; this considering that internal fat deposition increased with FA feeding in the current study. Thus, free FA could have modulated energy metabolism at environmental temperatures <35 °C to increase internal body fat reserves in case of glucose depletion (Macías-Cruz et al., 2020). These findings suggest that FA supplementation in heat-stressed hair ewe lambs causes a long-term change in body gain composition by favoring energy efficiency.

3.3.5.4. Carcass and non-carcass traits, wholesale cut yields and meat quality

Supplementation of free FA did not change carcass and non-carcass traits in our heat-stressed ewe lambs, which we attribute to non-constant growth stimulation through the feedlot phase due to variable extents of heat stress experienced by lambs in the different feeding periods. These findings agree with reports in hair ewe lambs (Macías-Cruz et al., 2014) and pigs (Li et al., 2015), but fed FA under thermoneutral conditions. In heat-stressed wool lambs, HCW and carcass yield were unaffected by using tannins and lycopene; also, with antioxidant properties (Jiang et al., 2015; Liu et al., 2016). Despite this, free FA increased internal fat deposition in our sheep, which supports a possible increase in blood insulin concentrations and lipogenic gene expression (Naowaboot, Piyabhan, Munkong, Parklak, & Pannangpetch, 2016) due to

FA under HS. A greater accumulation of internal fat in heat-stressed sheep represents an adaptive metabolic mechanism to have available energy in case of glucose depletion (Macías-Cruz et al., 2020).

In general, FA supplementation increased forequarter yield at a similar magnitude that it decreased hindquarter yield and, in consequence, this former beneficial effect of FA was not reflected in overall carcass weight and yield. However, most wholesale cut yields were improved by supplementing the FA, although neck, plain loin and leg yields decreased. This contrasts with findings previously published by our group at the same study site using hair ewe lambs in the absence of a thermal insult, i.e., no wholesale cut yield was affected by free FA (Macías-Cruz et al., 2014). This difference between studies suggests that there was an associative effect between HS conditions and FA supplementation to improve wholesale cut yields, mainly those directly involved in the respiratory tract function. Note that muscles, in consequence wholesale cuts, surrounding the ribcage have a higher proportion of oxidative than fast-glycolytic fibers (Ithurralde et al., 2015). Oxidative fibers compared with those fast-glycolytic have moderate to high fatigue resistance, insulin sensitivity, glucose oxidation, mitochondrial activity and ROS production (Yates et al., 2018). Indeed, both HS in sheep (Sejian et al., 2017) and FA in rats (Ghosh et al., 2017) have raised blood insulin levels and cell glucose uptake; additionally, the FA scavenges free radicals, promotes formation of slow oxidative fibers, and inhibits the activity of fast glycolytic fibers through Sirt1/MAPK pathway regulation (Chen et al., 2019). So, we hypothesized that improved metabolism in oxidative fibers due to combined effects of FA and HS led to muscle hypertrophy, which was reflected in higher yield of wholesale cuts where those muscle fibers predominated. Furthermore, as fast glycolytic fibers predominate in muscles of neck, plain loin and leg, it is likely that free FA supplementation can reduce muscle mass formation, and therefore, yields of those wholesale cuts.

That meat quality was not affected by feeding our ewe lambs with free FA under HS conditions is consistent with results in steers (González-Ríos et al., 2016) and pigs (Li et al., 2015) that were supplemented with FA in a thermoneutral environment. It should be noted that, as the ultimate pH, color and shear force in our

meats were within normal ranges (Corazzin, Del Bianco, Bovolenta, & Piasentier, 2019), this suggests that hair breed sheep under chronic HS adapt to hyperthermia conditions and decrease oxidative damage in skeletal muscle. Thus, it is likely that the meat did not present a high oxidation and, consequently, free FA did not exert its antioxidant effects (Kubik, Tietze, Schmidt, Yates, & Petersen, 2018).

3.3.6. Conclusions

Free FA supplementation of heat-stressed hair ewe lambs improved growth and feed efficiency only when Te exceeded 35 °C due to its antioxidant activity; then, when Te and oxidative stress began to decline, it exerted lipogenic action and changed the body gain composition. In addition, FA improved internal fat deposition and yields of most wholesale cuts. However, it failed to enhance carcass characteristics and meat quality. Beneficial results could be associated with lower protein oxidation and better function of the glucose-insulin system. Effects of FA feeding on energy metabolism of heat-stressed hair lambs should be demonstrated in future research.

3.3.7. References

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3.3.8. Tables and figures

Table 9. Ingredients and chemical composition of the basal diet.

Ingredient composition (% mixed basis)	
Alfalfa, hay	10
Wheat, straw	15
Wheat, grain ground	62
Soybean, meal	11
Premix, mineral/vitamin	0.5
Limestone	0.5
Dicalcium phosphate	0.5
Salt	0.5
Chemical composition (DM basis)	
Dry matter (%)[a]	90.5
Crude protein (%)	16.1
Ether extract (%)	3.5
Ash (%)	7.8
Acid detergent fiber (%)	18.0
Neutral detergent fiber (%)	25.7
Metabolizable energy (MJ/kg)[b]	12.4

[a] Only dry matter (DM) was calculated in mixed basis.

[b]Calculated using formulas from NRC (1985).

Table 10. Effects of ferulic acid on rectal temperature and respiratory rate during sampling days in heat-stressed hair ewe lambs.

Items	Treatments (T)[a]			Sampling days (D)						*P*-Values		
	Control	FA	SEM	1	10	20	30	40	SEM	T	D	T x D
Respiratory rate (breaths per minute)												
0600 h[c]	107.31	108.40	2.16	86.82	106.64	105.73	117.55	122.55	2.70	0.73	<0.01	0.11
1800 h[b]	173.50	170.50	1.83	157.48	159.64	185.73	190.64	167.00	2.62	0.30	<0.01	0.59
Rectal temperature (°C)												
0600 h[c]	39.80	39.78	0.06	39.86	39.93	39.67	39.85	39.70	0.05	0.93	<0.01	0.01
1800 h[b]	40.18	40.17	0.09	40.24	40.12	40.23	40.28	40.01	0.06	0.91	<0.01	0.15

[a] Ewe lambs fed 0 or 250 mg of free ferulic acid (FA) per kg of diet.

[b] Cubic effect due to sampling day.

[c] Quartic effect due to sampling day.

Table 11. Effects of ferulic acid on serum oxidative stress markets during sampling days in heat-stressed hair ewe lambs.

Items[b]	Treatments (T)[a]			Sampling days (D)				*P*-Values		
	Control	FA	SEM	1	20	40	SEM	T	D	T x D
MDA (µmol/L)[d]	1.60	1.36	0.13	1.93	1.21	1.30	0.12	0.20	<0.01	0.49
AOPP (µmol/L)[c]	7.25	6.59	0.26	8.94	6.73	5.08	0.20	0.06	<0.01	0.70
TOC (µmol Eq H_2O_2/L)[d]	6.40	6.16	0.50	10.32	4.27	4.24	0.45	0.74	<0.01	0.53
TAC (µmol Eq Trolox /L)[d]	1.96	1.13	0.15	1.83	0.71	0.94	0.15	0.76	<0.01	0.49
OSI (arbitrary units)[c]	0.62	0.57	0.06	0.68	0.62	0.47	0.05	0.52	<0.01	0.18

[a] Ewe lambs fed 0 or 250 mg of free ferulic acid (FA) per kg of diet.

[b] MDA=Malondialdehyde, AOPP= Advanced oxidation protein products, TOC= Total oxidant capacity, TAC= Total antioxidant capacity, OSI= oxidative stress index.

[c] Linear effect due to sampling day.

[d] Quadratic effect due to sampling day.

Table 12. Effects of ferulic acid on overall feedlot performance of heat-stressed hair ewe lambs.

Items	Treatments[a]		SEM	*P*-Values
	Control	FA		
Initial body weight (kg)	23.61	23.46	0.19	0.60
Final body weight (kg)	30.97	30.97	0.31	1.00
Total body weight gain (kg)	7.36	7.51	0.26	0.70
Daily weight gain (kg)	0.185	0.189	0.006	0.71
Dry matter intake (kg)	1.08	1.09	0.02	0.78
Feed efficiency (kg/kg)	0.170	0.175	0.005	0.39
Water intake (L/d)	4.78	5.09	0.24	0.38

[a] Ewe lambs fed 0 or 250 mg of free ferulic acid (FA) per kg of diet.

Table 13. Effects of ferulic acid on carcass characteristics and body fat deposition of heat-stressed hair ewe lambs.

Items	Treatments[a]		SEM	*P*-Values
	Control	FA		
Hot carcass weight (kg)	14.73	14.55	0.18	0.48
Cold carcass weight (kg)	14.29	14.16	0.19	0.65
Hot carcass yield (%)[b]	60.86	61.04	0.67	0.85
Cold carcass yield (%)[b]	59.02	59.48	0.57	0.58
Conformation (units)	6.41	6.36	0.23	0.89
MLT area (cm^2)[c]	11.86	11.04	0.56	0.32
Morphometric measures (cm)				
Carcass length	55.23	54.82	0.59	0.63
Thorax Depth	14.95	15.57	0.25	0.11
Leg length	24.18	24.27	0.38	0.87
Leg perimeter	40.75	39.55	0.43	0.07
Body fat				
Fat thickness (mm)	2.32	2.95	0.28	0.14
KPH (%)[d]	2.15	2.71	0.19	0.03
Omental (%)[b]	2.31	2.65	0.19	0.23
Mesenteric (%)[b]	1.78	2.21	0.11	0.02

[a] Ewe lambs fed 0 or 250 mg of free ferulic acid (FA) per kg of diet.

[b] Calculated expressing weights as a percentage of empty body weight.

[c] MLT area= *Longissimus thoracic* muscle area.

[d] KPH= Kidney-pelvic-heath fat, expressed as a percentage of hot carcass weight.

Table 14. Effects of ferulic acid on wholesale cut yields of heat-stressed hair ewe lambs.

Items[b]	Treatments[a]		SEM	*P*-Values
	Control	FA		
Forequarter (%)	51.75	53.66	0.46	0.01
Hindquarter (%)	48.25	46.33	0.46	0.01
Neck (%)	4.53	3.95	0.16	0.03
Loin (%)	11.70	12.35	0.27	0.10
Ribs (%)	8.18	8.80	0.23	0.08
Shoulder (%)	27.35	28.57	0.32	0.02
Plain loin (%)	11.25	10.48	0.24	0.04
Breast and flank (%)	5.45	6.21	0.23	0.04
Leg (%)	31.54	29.64	0.51	0.02

[a] Ewe lambs fed 0 or 250 mg of free ferulic acid (FA) per kg of diet.

[b]Weights expressed as a percentage of the half carcass.

Table 15. Effects of ferulic acid on weights of non-carcass components of heat-stressed hair ewe lambs.

Items[b]	Treatments[a]		SEM	*P*-Values
	Control	FA		
Blood (%)	5.46	5.68	0.18	0.39
Skin (%)	9.79	10.27	0.37	0.38
Head (%)	6.08	6.24	0.11	0.33
Feet (%)	2.89	2.91	0.04	0.72
Heart (%)	0.57	0.60	0.02	0.46
Kidney (%)	0.37	0.39	0.01	0.18
Liver (%)	2.26	2.26	0.04	0.90
Spleen (%)	0.22	0.23	0.01	0.95
Lungs (%)	1.52	1.43	0.04	0.14
Empty GT[c] (%)	7.33	7.29	0.19	0.90

[a] Ewe lambs fed 0 or 250 mg of free ferulic acid (FA) per kg of diet.

[b] Weights expressed as a percentage of the empty body weight.

[c] Empty GT= Empty gastrointestinal tract.

Table 16. Effects of ferulic acid (FA) on meat quality of the *Longissimus thoracis* (LT) muscle of heat-stressed hair ewe lambs.

Items	Treatments[a]		SEM	*P*-Values
	Control	FA		
pH *postmortem*				
45 min	6.36	6.33	0.02	0.36
Ultimate (24 h)	5.73	5.70	0.02	0.26
Meat quality after aging[b]				
pH	5.72	5.68	0.03	0.11
Lightness (L*)	44.27	43.75	0.77	0.64
Redness (a*)	19.60	19.73	0.15	0.58
Yellowness (b*)	5.75	5.73	0.23	0.96
Hue angle (H*)	16.31	16.20	0.61	0.90
Chroma (C*)	20.44	20.57	0.17	0.62
WBSF[c] (N)	34.90	35.67	0.97	0.59

[a] Ewe lambs fed 0 or 250 mg of free ferulic acid (FA) per kg of diet.

[b] LT muscle was dissected, vacuum packed and aged during 14 d between 0 - 4 °C.

[c] WBSF= Warner-Bratzler shear force.

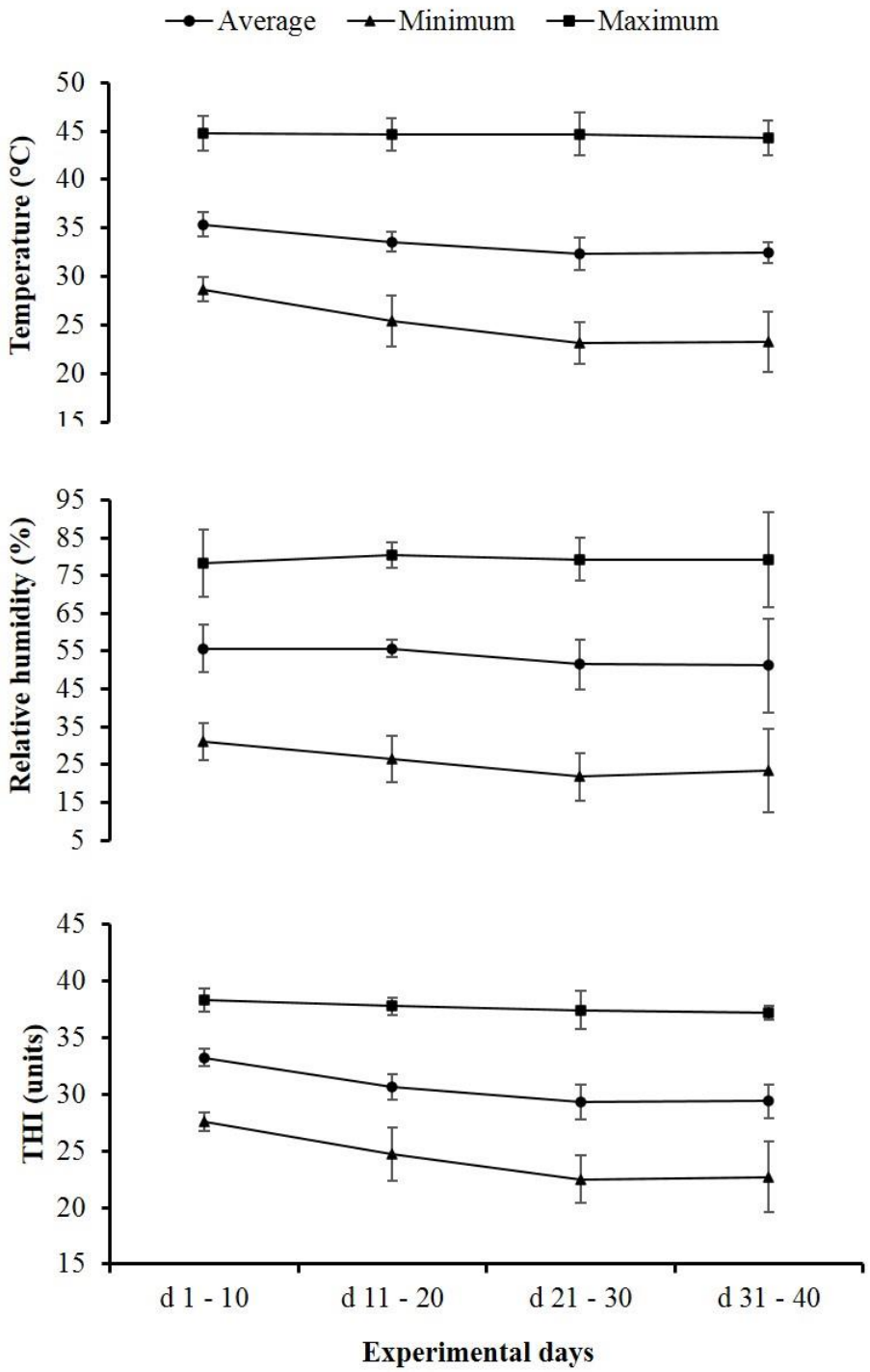

Figure 4. Temperature, relative humidity, and temperature-humidity index (THI) for 10-d periods during the feedlot phase.

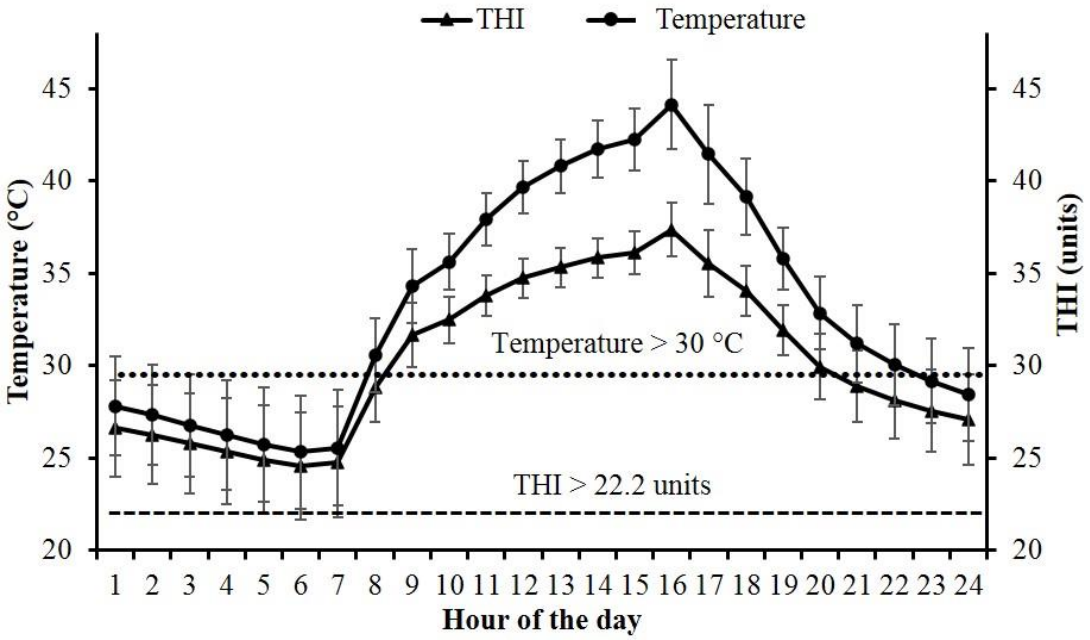

Figure 5. Diurnal patterns for temperature (Te) and temperature-humidity index (THI) during the feedlot phase (mean ± SD). Non-continuous lines indicate the upper limit of Te (····) and THI (– – –) considered as thermoneutral.

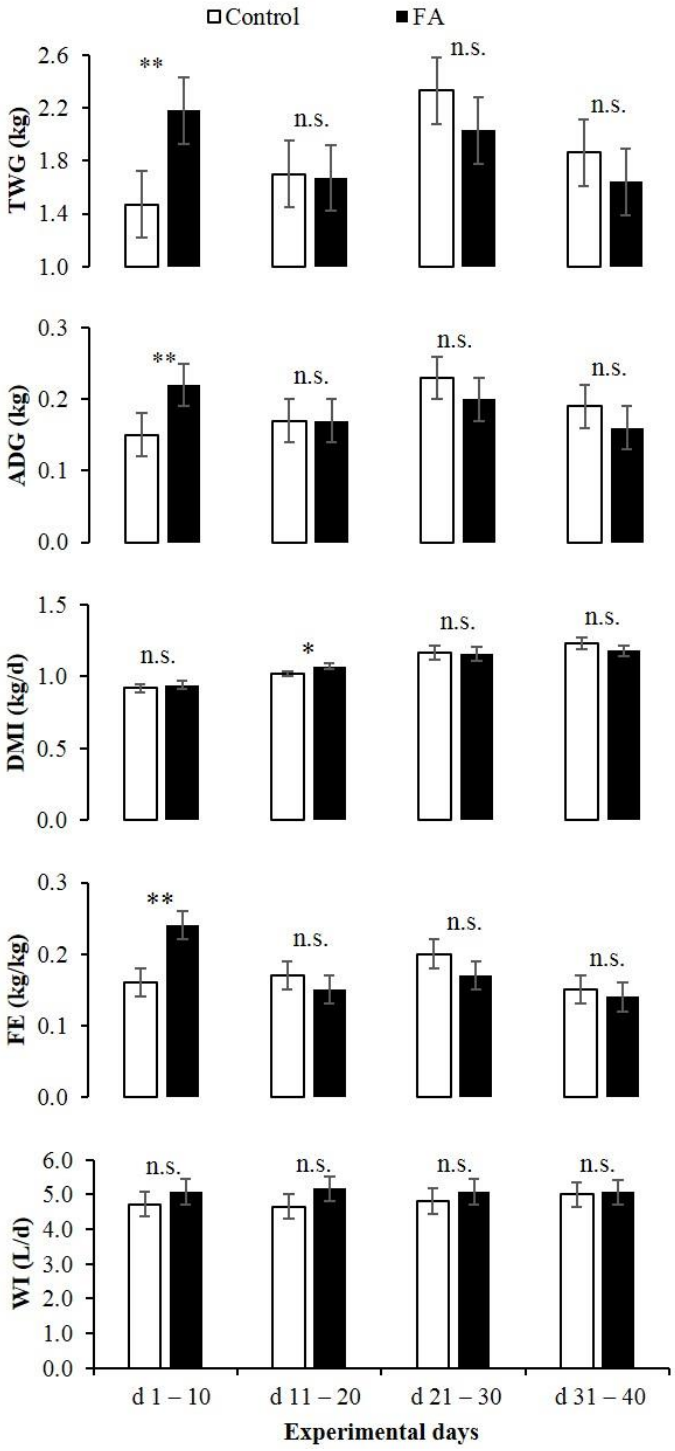

Figure 6. Effects of ferulic acid (FA) on feedlot performance of heat-stressed hair ewe lambs by period [TWG= total body weight gain; ADG= average daily gain; DMI= dry matter intake; FE = feed efficiency; WI= water intake]. * P<0.05, ** P <0.01 and n.s. P>0.05.

CAPÍTULO IV. CONCLUSIONES GENERALES

En general, los resultados del presente estudio demuestran que el EC promovió la presencia de estrés oxidativo en corderas de pelo en crecimiento. Los factores que determinaron las variaciones en los biomarcadores séricos de estrés oxidativo y respuesta antioxidante fueron las condiciones climáticas, FR y el crecimiento de las corderas. Específicamente, rangos de Ta, HR e ITH de 22.6 a 34.6°C, 17.7 a 82.3% y de 22.4 a 31.5 unidades, respectivamente, y la insulina sérica se correlacionaron positivamente con el daño oxidativo (MDA, PAOP, capacidad oxidante total e IEO) y con la capacidad antioxidante total. No obstante, a partir de una Ta de 41.2° C, de un ITH de 35.3 unidades y de incrementos en la FR de la mañana, se observó una disminución en la respuesta oxidante y antioxidante. De tal modo que dichos indicadores contribuyeron negativamente a variaciones séricas del MDA y capacidad oxidante total (Ta), de la capacidad antioxidante total (ITH) y de PAOP (FR de la mañana). Con respecto a la HR, esta contribuyó positivamente a explicar cambios en el IEO. En menor grado, la concentración sérica de insulina, el consumo de alimento y la GDP fueron factores que también contribuyeron a incrementar PAOP, la capacidad oxidante total y el IEO, respectivamente.

El estrés oxidativo que presentaban las corderas fue parcialmente mitigado por la suplementación de AF. Si bien el AF no afectó la capacidad oxidante y antioxidante total, IEO y MDA sérico generados por los factores anteriormente mencionados, sí favoreció la disminución de PAOP. Asimismo, posiblemente asociado a su acción antioxidante sobre proteínas, el AF aumentó más del 46% la GDP y eficiencia alimenticia bajo condiciones extremas de EC (Ta > 35°C) y la deposición muscular del cuarto delantero de la canal (particularmente en cortes localizados alrededor de la región torácica). Adicionalmente, la suplementación de dicho fenol disminuyó la hipertrofia muscular en regiones del cuarto trasero e incrementó las reservas de grasa interna. Sin embargo, a pesar de los cambios que promovió en la deposición de tejido adiposo y muscular, el AF no afectó las características de la canal y calidad de la carne.

En conjunto, los hallazgos obtenidos sugieren la importancia de la evaporación respiratoria y la activación de mecanismos citoprotectores en ovinos de pelo en

crecimiento bajo condiciones extremas de EC. Lo anterior pudo estar reforzado parcialmente por el AF al mejorar el desarrollo de músculos involucrados en la acelerada actividad respiratoria que presentaban los animales para disipar calor y al disminuir la oxidación proteica. Respuestas que, a su vez, se reflejaron en un mayor crecimiento bajo condiciones de Ta > 35°C y en la conservación de las características de canal y calidad de la carne. Adicionalmente, el AF incrementó la disponibilidad de energía en corderos de pelo estresados al aumentar las reservas de grasa interna. Futuras investigaciones deberán dilucidar las respuestas celulares que activan los corderos de pelo estresados por calor para contrarrestar el estrés oxidativo bajo condiciones extremas de EC, así como la intervención del AF sobre ellas y sobre vías lipogénicas.

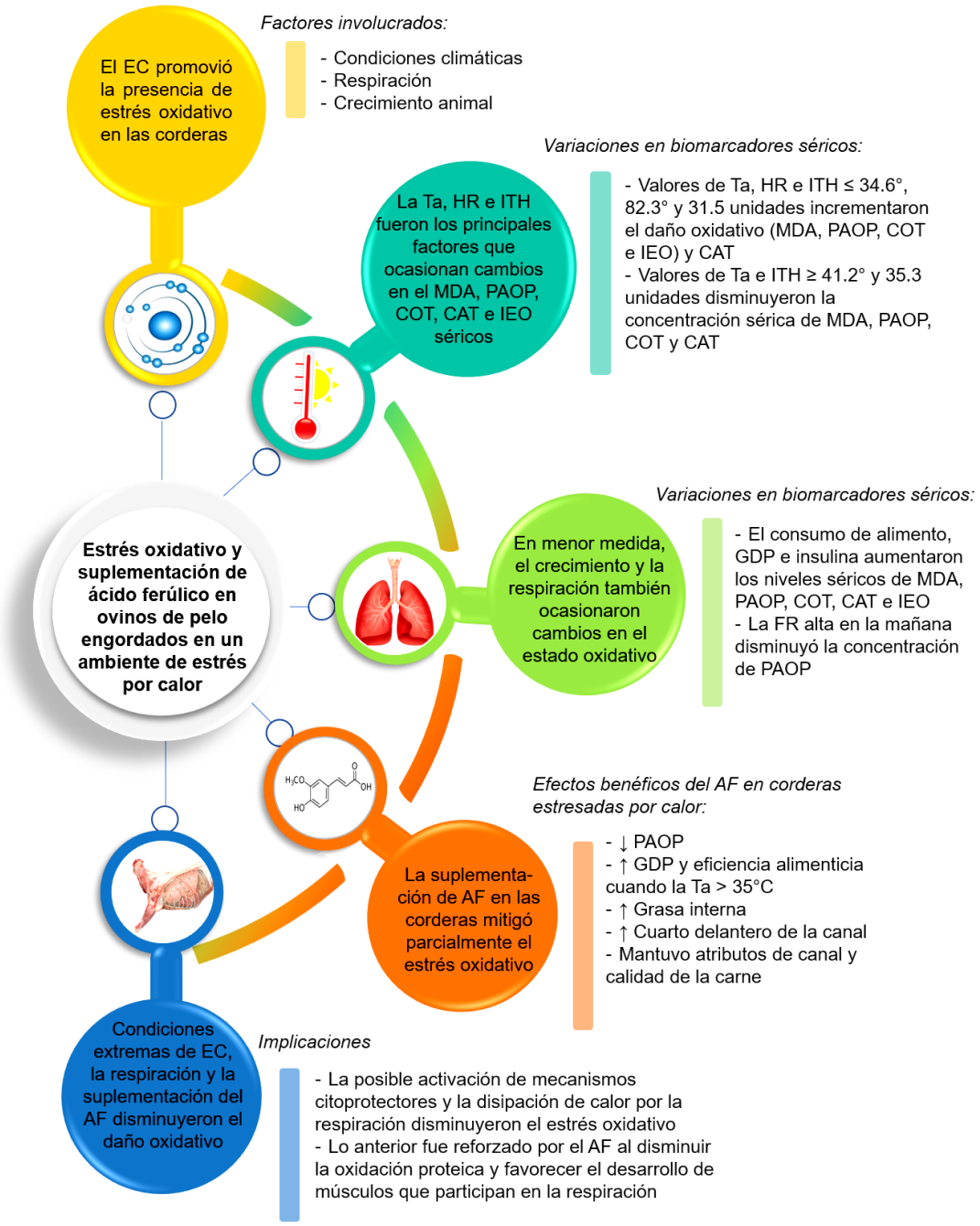

Figura 7. Resumen gráfico de conclusiones generales. EC= estrés por calor; Ta= temperatura ambiente; HR= humedad relativa; ITH= índice de temperatura-humedad; MDA= malondialdehído; PAOP= productos avanzados de la oxidación proteica; COT= capacidad oxidante total; CAT= capacidad antioxidante total; IEO= índice de estrés oxidativo; GDP= ganancia diaria de peso; FR= frecuencia respiratoria; AF= ácido ferúlico.

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Ferulic acid in animal feeding: Mechanisms of action, productive benefits, and future perspectives in meat production

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ABSTRACT

The livestock sector's major challenge is to meet the growing demand for foods of animal origin without compromising animal welfare and human health. In this effort to produce more efficiently and ethically, researchers have currently been focused on the study of phytochemicals with nutraceutical properties in order to improve meat production. Ferulic acid (FA) is a phenolic compound that is attracting special interest in the livestock sector due to its multiple benefits associated with its antioxidant, cytoprotective, antimicrobial, and anabolic properties. The activation of these mechanisms stimulates and/or favors physiological and metabolic processes, and consequently, farm animals' growth and reproduction. Thus, FA ingestion could improve feedlot performance, carcass characteristics, and meat quality, as well as gonad-gamete activity. However, the information available is controversial. Therefore, this review aimed to summarize current information about the mechanisms of action of FA and its benefits on productive and reproductive aspects, highlighting new possible applications of this phytochemical in the meat production chain.

1. Introduction

According to projections, the world population will reach 9.1 billion people in 2050; it will also increase the demand for animal-source foods by approximately 75% (Baldi & Gottardo, 2017). In this context and under the approach of a "clean, green and ethical" production (Sneddon, 2009) the current animal production systems must guarantee food safety without compromising both animal welfare and human health (Lillehoj et al., 2018). As a result, a natural strategy to increase animal protein production is the use of phytochemicals with nutraceutical properties instead of synthetic antimicrobials, growth promoters, or hormones (Hashem, González-Bulnes & Simal-Gandara, 2020; Macías-Cruz et al., 2018; Marquardt & Li, 2018).

Phytochemicals are bioactive compounds produced during the plant metabolism that can improve animal productivity by exerting different mechanisms of action (Kumar & Goel, 2019). The most abundant phytochemicals are hydroxycinnamic acids, phenolic compounds with powerful antioxidant activity that favorably mediate different physiological and metabolic processes (Peña-Torres et al., 2019). Currently, the ferulic acid (FA) is a phenol of special interest in the livestock sector since its antioxidant, antimicrobial, and anabolic properties may generate health, productive, and reproductive benefits in farm animals (González-Ríos et al., 2016; Li et al., 2015; Macías-Cruz et al., 2018; Valadez-García et al., 2021; Wang, Wang, et al., 2019).

The dietary supplementation of FA in fattening animals increases muscle deposition and feed efficiency (Herrera, Alejo, & Asaff, 2011; Valadez-García et al., 2021; Wang, Wang, et al., 2019,b), and improves meat quality and shelf life (González-Ríos et al., 2016; Li et al., 2015). Concerning reproductive efficiency, FA induces endocrine and exocrine activity in gonads, reproductive tract development (Macías-Cruz et al., 2018; Moshfegh, Baharara, Namvar, Zafar-balanezhad, & Amini, 2016), *in vitro* maturation, fertilization of oocytes (Lee & Hyun, 2017; Tanihara et al., 2018) and semen cryopreservation (Affonso et al., 2017). However, in some cases, the benefits described as an effect of FA across the literature are sometimes inconsistent (González-Ríos et al., 2016; González-Ríos, Gil, & Berrondo, 2013; Li et al., 2015; Macías-Cruz et al.,

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2014). Therefore, this review aimed at summarizing current information about the mechanisms of action of FA and its benefits on productive and reproductive aspects, highlighting new possible applications of this phytochemical in the meat production chain.

2. Generalities and Importance as a functional Ingredient

The FA is the most abundant phenolic compound from the group of hydroxycinnamates and is found as part of the cell wall of plants, fruits, vegetables feedstuffs and cereal grains (Cao, Jin, Yang, Li, & Jiang, 2015; de Paiva, Goldbeck, Dantas, & Squina, 2013). This phenol was first isolated from *Ferula foetida* in 19th century and chemically described in 1925 (de Oliveira Silva & Batista, 2017). The FA [(E) -3-(4-hydroxy-3-methoxy-phenyl) propyl-2-enoic acid] presents *cis*- and *trans*-isomerism being the *cis*-isomer a yellow oily liquid and the *trans*-isomer (the most abundant in nature) a white crystal (de Paiva et al., 2013; Kuppusamy, Soundharrajan, Kim, Hwang, & Choi, 2019). Overall, it is soluble in water, ethyl acetate, ethanol, and ethyl ether, sensible to isomerization by sunlight (Bento-Silva, Vaz, & Bronze, 2018), and has a melting point of 168–171 °C and molar mass of 194,186 g mol^{-1} (National Center for Biotechnology Information, 2019).

In plants, FA is a secondary metabolite synthesized in the shikimate/phenylpropanoid pathway to give stiffness and protection (de Oliveira Silva & Batista, 2017). So, it is part of the cell wall's structural composition where is found free, dimerized and linked by ester and ether bonds with lipids, carbohydrates and lignin (de Paiva et al., 2013). Both free and bound FA can be released from natural sources by different extraction methods (Mancuso & Santangelo, 2014). While free FA needs aqueous or organic solvents to be extracted (e.g., methanol), bound FA requires chemical alkaline or enzymatic hydrolysis treatments to break covalent bonds with the other cell wall components. Depending on the extraction method and operating conditions (e.g., room temperature, pH, and time), free FA or different bioactive derivatives can be released (Bento-Silva, Vaz Patto, & do Rosário Bronze, 2018).

The FA is a functional ingredient because it has beneficial effects on human health associated with its antioxidant action (Kumar & Pruthi, 2014; Kuppusamy et al., 2019). Thus, this phenol acts as an anti-inflammatory, hepatoprotective, antidiabetic, anticholesterolemic, anticancer, neuroprotective, and UV protector agent (de Oliveira Silva & Batista, 2017). Furthermore, studies in murine models suggest that FA may be useful to treat obesity and infertility in humans (Kuppusamy et al., 2019; Salazar-López et al., 2017). In addition, it is valuable in the manufacture of medicines, cosmetics, and nutraceuticals. Taking advantage of the fact that FA is a nutraceutical additive, in the last decade several research groups throughout the world have been evaluating this phenolic compound with the aim of improving animal production (Ma et al., 2020; Macías-Cruz et al., 2018; Valadez-García et al., 2021; Wang et al., 2021).

3. Pharmacokinetics and bioavailability

The biological effectiveness of FA depends on its bioaccessibility from the food matrix and how it is absorbed, metabolized, and transported to the host's target tissues, i.e., its pharmacokinetics (Phan et al., 2020). As the majority of the plant-based polyphenols, the FA is poorly absorbed in the gastrointestinal tract (GIT) due to its esterified form in the cell wall (Adam et al., 2002). Consequently, supplementation of livestock with free FA or its derivatives is necessary to ensure its bioavailability and biological effectiveness (Cao et al., 2015).

3.1. Non-ruminants

Studies of FA pharmacokinetics in non-ruminants are limited to murine models. Ferulic acid in its free form is more bioavailable after ingested than FA as a component of the food matrix (Sova & Saso, 2020). The esterase enzymes action in the stomach is not efficient in releasing FA bound to the food matrix, and in consequence, only a small part of the total ingested FA is absorbed in the upper gut (Mancuso & Santangelo, 2014). The metabolism of absorbed FA takes place mainly in liver where the hydroxyl group is conjugated by glucuronidation and sulfation reactions (Kumar & Goel, 2019). After metabolism, albumin transports small or undetectable concentrations of conjugated FA through the bloodstream toward target tissues to exert its biological effects, and finally the metabolized FA via urine is excreted (Adam et al., 2002). On the other hand, non-released FA in stomach continues its passage to the large intestine, where the cecal microbiota transforms it into 3- (3-m-hydroxyphenyl) propionic acid for a higher hepatic β-oxidation. It is noteworthy that there is unreleased FA that is excreted directly in feces (de Paiva et al., 2013).

In contrast to FA from the food matrix, the free FA supplemented to animals is more bio-accessible and bioavailable because its absorption occurs in small intestine across monocarboxylic transporters (Sova & Saso, 2020). It is estimated that around 56% of free FA ingested crosses the intestinal barrier and reaches the liver through the portal system for metabolism (Adam et al., 2002). However, only 50% of this metabolized FA is bioavailable to tissues and the remaining 6% is excreted in feces through biliary activity. The circulating blood concentration of this phenol reaches its peak within 30 min (Mancuso & Santangelo, 2014) and more than 90% of its excretion through urine occurs in the first 6 h post-ingestion (Kishida & Matsumoto, 2019).

3.2. Ruminants

In ruminants as in monogastric animals, FA from the feed matrix is less bio-accessible and bioavailable than in its free form. Forages and cereals used to feed ruminants are natural sources of FA (Table 1), but very little of this compound escapes from ruminal enzymatic activity (Soberon, Cherney, & Cherney, 2012). Once cell wall's breakdown occurs by the action of cellulolytic ruminal bacteria, microbial enzymes immediately transform most of the released FA into 3-phenylpropionic by hydrogenation-dihydroxylation reactions (Chesson et al., 1999). This 3-phenylpropionic is absorbed and metabolized in liver to benzoic acid, and finally excreted in urine as hippuric acid (Peña-Torres et al., 2019). The FA that escapes from microbial action may also be absorbed and conjugated in liver; however, its concentration in plasma and urine is almost undetectable (Soberon, Cherney, Liu, Ross, & Cherney, 2012).

On the contrary, the free FA offered through the diet to lactating cows had a rapid absorption after ingestion with maximum concentration in plasma and urine at 15 min and 2.7 h, respectively, but returning to basal concentrations at 5.5 h in plasma and 14 h in urine (Soberon, Cherney, Liu, et al., 2012). Similarly, Soberon, Cherney, and Cherney (2012) reported in free FA-fed sheep a reduction in circulating FA concentration within the first 5 h post-ingestion, being the urine the main route of excretion. Overall, these findings suggest that free FA is well absorbed and rapidly bioavailable in monogastric and ruminant animals but has a short time of availability. Therefore, future studies should establish both optimal dosage and supplementation frequency of FA to ensure prolonged action; in addition, researchers should consider

Table 1
Ferulic acid concentration in main feedstuffs used in animal diets.

Ingredient	Concentration (mg/g)	Reference
Alfalfa hay	1.5–2.6	Soberon, Cherney, and Cherney (2012)
Corn stover	5.3	Cao et al. (2015)
Corn silage	5.8	Cao et al. (2015)
Oat bran	0.33	Boz (2015)
Rye bran	2.8	Zhao and Moghadasian (2008)
Wheat bran	13.5–14.5	Zhao and Moghadasian (2008)
Corn grain	2.6–34	Bento-Silva et al. (2018)
Oat grain	0.25–0.35	Boz (2015)
Wheat grain	13–14	de Paiva et al. (2013)
Soy meal	0.12	Kumar and Pruthi (2014)

differences among species, breeds, and physiological state.

4. Mechanisms of action in livestock

Supplemental FA improves livestock productivity by exerting multiple mechanisms of action. The first mechanisms involve its action as cytoprotective product (Mancuso & Santangelo, 2014) and adrenergic agonist (González-Rios et al., 2016), although the latter is a very controversial issue. More recently, some studies suggest that it can also act as an antimicrobial agent (Ma et al., 2020; Shi et al., 2016), as well as intervene in muscle and gonadal activity by regulating gene expression (Chodkowska, Ciecierska, Majchrzak, Ostaszewski, & Sadkowski, 2018) and intracellular signaling pathways (Kuppusamy et al., 2019). Information on farm animals continues to be scarce, so more studies should be carried out to elucidate the different paths that this phenolic compound employs to induce biological effects.

4.1. Cytoprotective mechanisms

The FA acts as a bifunctional antioxidant in the presence of oxidative stress since it can directly eliminate free radicals and regulate the cellular antioxidant enzyme activity (Zhao & Moghadasian, 2008). The first function is associated with the chemical structure of this phenol as its phenolic hydroxyl group donates one hydrogen atom to free radicals for the formation of stabilized phenoxy radicals (Frankel, 2012, pp. 209–258). The second function is attributed to the fact that FA upregulates the expression of antioxidant enzymes (i.e., catalase, glutathione peroxidase, and superoxide dismutase) by activating the nuclear factor erythroid 2-related factor 2/antioxidant responsive element pathway (Nrf2/ARE; Mancuso & Santangelo, 2014). In this way, FA decreases the overproduction of reactive oxygen species (ROS) and increases antioxidant defense, leading to less oxidative damage of biomolecules (Ghosh, Basak, Dutta, Chowdhury, & Sil, 2017).

Other cytoprotective mechanisms exerted by FA include the upregulation of heat shock protein (HSP) expression and the avoidance of activation of apoptotic pathways(de Oliveira Silva & Batista, 2017). *In vitro* and *in vivo* studies have shown that FA increases the HSP32 and HSP70 expression (Ghosh et al., 2017; Hussein, Abbas, Abulseoud, & El-Hussainy, 2017; Ma, Hong, Wang, Liang, et al., 2011; Shi et al., 2016; Song et al., 2014), proteins that decrease free radicals production (HSP32; Ma, Hong, Wang, Liang, et al., 2011) and prevent protein oxidation and catabolism (HSP70; Hussein et al., 2017). The anti-apoptotic action of FA is attributed to the activation of the Nrf2/ARE pathway (Song et al., 2016), the upregulation of anti-apoptotic gene expression (Chodkowska et al., 2018), or the direct binding of FA to cytochrome C to keep it stable (Yang et al., 2007).

Thus, by exercising the aforementioned cytoprotective actions, FA protects cells' structural and functional integrity (Hussein et al., 2017). In this sense, several studies carried out with laboratory and/or farm animals report that FA mitigates oxidative stress effects in enterocytes (He et al, 2016, 2018), hepatocytes (Song et al., 2014; Yu et al., 2018), β-cells in the pancreas (Ramar et al., 2012; Roy, Metya, Rahaman, Sannigrahi, & Ahmed, 2014; Salazar-López et al., 2017; Wang et al., 2015), cardiac cells (Song et al., 2014), muscle fibers (Li et al., 2015; Valadez-García et al., 2021), neurons (Hussein et al., 2017), lymphocytes (Ma, Hong, Wang, Liang, et al., 2011), erythrocytes (Ma, Hong, Wang, Tan, et al., 2011), Leydig cells (Hasanein, Fazeli, Parviz, & Roghani, 2018), gonads (Salma, Abdel, Karam, & El Hameed, 2019), and embryonic cells (Tanihara et al., 2018). Therefore, FA could improve physiological, metabolic, and immunological processes in animals with oxidative stress associated with stressors such as diseases, thermal stress, mobilization, others.

4.2. Adrenergic mechanisms

Free FA supplementation has been recommended as a natural alternative to the use of β-adrenergic agonists (β-AA) due to its possible β-adrenergic mechanisms (Valenzuela-Grijalva, Pinelli-Saavedra, Muhlia-Almazan, Dominguez-Díaz, & González-Rios, 2017). Due to its similarity in chemical structure to epinephrine and norepinephrine, studies carried out in cattle and pigs suggest that this phenol can bind to β2 adrenergic receptors and exert the same biological responses as a synthetic β-AA (González-Rios et al., 2013; Peña-Torres et al., 2019). Thus, FA may stimulate the release of growth hormone (GH) and prolactin (Gorewit, 1983) at level of adenohypophysis and promote an anabolic action on muscle fibers (Herrera et al., 2011; Peña-Torres et al., 2021). So far, this is only a hypothesis and more research is required to confirm it. In nature, there are many similar-looking molecules but with totally different biological actions.

Valenzuela-Grijalva et al. (2017) mentioned that FA could inhibit the enzyme catechol-O-methyltransferase, which degrades epinephrine and norepinephrine. So, FA can increase serum catecholamine concentrations and, in consequence, their biological effects (Yalcin & Bayraktar, 2010). However, the lack of molecular evidence to support these mechanisms of action in farm animals, together with results in rats suggesting an antagonistic effect of FA on β_1 and β_2 receptors (Wu et al., 1998), leading to the implementation of additional studies on the possible activity of FA as β-AA.

4.3. Antimicrobial mechanisms

In vitro (Gong et al., 2019) and *in vivo* (Wang et al., 2019 ab) assays evidenced that this phenol modulates intestinal and ruminal bacterial populations and may be helpful to treat pathogenic microorganisms (Borges, Ferreira, Saavedra, & Simões, 2013). According to Gong et al. (2019), FA in free form or bound to oligosaccharides stimulates the population growth of the enteric beneficial family *Biftdobacteriaceae* by acting as a fermentation substrate. Because of this change in the microbiota, FA also decreases the bacterial family *Enterobacteriaceae* population, microorganisms associated with amino acid degradation and GIT diseases. So, FA may promote better GIT health and higher microbial protein synthesis, as was recently proposed in lambs (Wang et al., 2019 ab). However, additional studies will be required to understand the complex interactions between FA and GIT microbiota, as well as implications in farm animals' health and productivity.

On the other hand, FA can be a natural alternative in treating common bacterial and viral diseases of economic importance in livestock. Studies with bacteria cultures (Borges et al, 2012, 2013; Saavedra et al., 2012) have shown that FA has an antimicrobial effect on strains of *Escherichia coli, Pseudomonas aeruginosa, Listeria monocytogenes*, and *Staphylococcus aureus* that cause neonatal colibacillosis, urogenital infections, meningitis, and mastitis in farm animals (Smith, 2010). So, by altering the surface physicochemical properties and the cytoplasmic membrane integrity of these bacteria, this phenol compound causes cytoplasm hyperacidification, producing irreversible structural changes and cell death (Borges et al., 2013). Porcine parvovirus, a primary cause of sows' reproductive failure, is another disease that can be treated with FA (Smith, 2010). Ma et al. (2020) showed in a culture of porcine kidney cells that FA markedly prevented the ROS overproduction, inflammation, and apoptosis caused by the porcine parvovirus suppressing the Nuclear Factor-κB inflammasome axis and Toll-Like Receptor 4.

4.4. Mechanisms associated to differentiation of muscle fibers

The type of muscle fibers that animals develop in the prenatal stage largely defines the muscle development capacity and, consequently, the meat quality (Du, Wang, Xing, Yang & Zhu, 2015). Using mouse myoblasts of the C2C12 line, *in vitro* studies have shown that FA is involved in the differentiation and proliferation process of myoblasts (Chen et al., 2019; Kuppusamy et al., 2019). Kuppusamy et al. (2019) stated that FA stimulates the differentiation of C2C12 cells by regulating the expression of bone morphogenetic proteins, as well as activation of the protein

kinase B pathway (PKB or Akt) and extracellular signal-regulated kinases (ERK). Moreover, Chen et al. (2019) observed that FA triggers a preferential differentiation in muscle toward slowly oxidizing muscle fibers (type I) that are positively correlated with insulin sensitivity and improved meat quality. The mechanism involved in this function was the activation of the signaling pathway sirtuin 1 - adenosine monophosphate-activated protein kinase (Sirt1/AMPK).

4.5. Molecular mechanisms associated to muscle hypertrophy

Beside its effect similar to β-AA, FA could promote muscle hypertrophy in fattening animals due to its ability to regulate signaling pathways and myogenic gene expression. Supplemental FA increases the slow-twitch fiber proportion in the *Longissimus thoracic* muscle (LTM) of weaned piglets due to the Sirt1/AMPK/PGC-1α pathway activation and improved mitochondrial function (Wang et al., 2021). In addition, FA activates the phosphatidylinositol 3 kinase/protein B kinase (PI3K/PKB or Akt) pathway in a similar way to the insulin-like growth factor I (IGF-I), which is reflected in higher muscle fiber diameter (Kuppusamy et al., 2019; Yeh, Hsu, Yang, Hsu, & Liu, 2014). At the level of myogenic gene expression, supplemental FA increased the transcription of myogenic regulatory factors (i.e., MyoD and myogenin) in zebrafish, obtaining better morphometric characteristics for skeletal muscle and higher body weight (Wen & Ushio, 2017). In horse satellite cells, it was reported that gamma oryzanol (compound rich in ferulate) stimulated higher cell proliferation and synthesis of sarcomeric proteins by regulating the expression of different genes associated with metabolic (*scd*), growth (*elavl1* and *Igf1r*), antioxidant (*nf2r2*), and anti-apoptotic (*Igf2*) activities (Chodkowska et al., 2018). However, these findings are still limited, so it is necessary to carry out more *in vivo* studies using production animals to verify the efficacy of FA, not only on transcription but also on the translation and expression of sarcomeric proteins, and consequently, on muscle hypertrophy.

5. Effects on animal metabolism

The FA has been shown to modulate animal metabolism mainly due to its cytoprotective capacity. In rats with high oxidative stress, FA improved insulin synthesis in pancreatic β cells due to its antioxidant and anti-inflammatory properties (Ramar et al., 2012; Roy et al., 2014; Salazar-López et al., 2017; Song et al., 2014; Wang et al., 2015). Similarly, Macías-Cruz et al. (2018) reported changes in the glucose-insulin system for pre-pubertal ewes fed free FA, particularly a reduction in serum glucose concentrations associated with high insulin synthesis. Meanwhile, FA-supplemented heifers had high GH production (Gorewit, 1983), which in turn could have stimulated a higher production of hepatic IGF-I (Chodkowska et al., 2018). It is noteworthy that feeding ruminants with FA does not affect serum triiodothyronine or thyroxine concentrations under thermoneutral conditions (Gorewit, 1983; Macías-Cruz et al., 2018), but does in a hot environment. In fact, heat-stressed hair ewe lambs receiving supplemental FA had lower serum thyroxine concentration and oxidative stress index without altering serum triiodothyronine concentrations compared to control group (Valadez-García, 2019). The authors associated this finding with FA beneficial action on aerobic metabolism by an increased antioxidant defense, improved mitochondrial function, and higher thyroxine deiodination. If further studies confirm these mechanisms, the dietary supplementation of free FA could become a strategy to mitigate heat stress in small ruminants.

According to the aforementioned findings, it can be inferred that FA affects metabolic routes of the major nutrients, and consequently, favors both animal reproduction and growth (Fig. 1). Concerning carbohydrate metabolism, free FA has demonstrated to stimulate cellular glucose uptake while maintaining euglycemia in sheep subjected to different environmental conditions (Macías-Cruz et al., 2018; Valadez-García, 2019; Wang et al., 2019 ab), as well as in hyperglycemic mice (de Oliveira Silva & Batista, 2017; Ramar et al., 2012; Roy et al., 2014). Perhaps, this adjustment in glucose metabolism due to FA is the result of increased circulating insulin concentration and the translocation of glucotransporters (GLUT4) towards the cell membrane (Kumar & Goel, 2019; Naowaboot et al., 2018), which in turn favors energy metabolism in tissues such as skeletal muscle (Chen et al., 2019; Chodkowska et al., 2018). Notably, this is a key response for animal reproduction and growth because glucose is the main energy source used by gonads and muscles.

The FA also could have anti-hyperlipidemic effects in obese farm animals as it decreases the biosynthesis of fatty acids, triglycerides, and cholesterol esters according to studies carried out with mouse C2C12

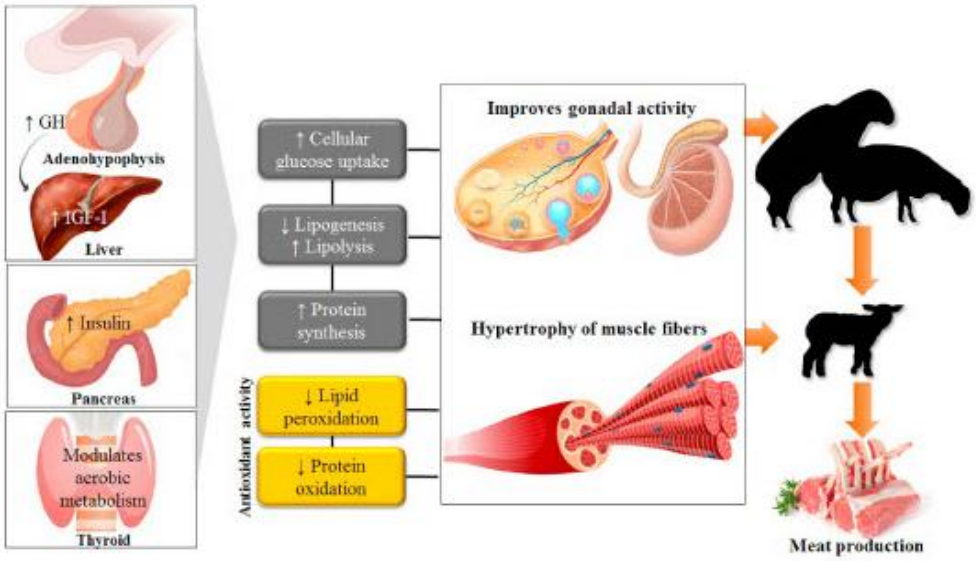

Fig. 1. Effects of ferulic acid in animal metabolism (endocrine and cellular level) and implications in gonads and skeletal muscle function. GH = growth hormone; IGF-I = insulin-like growth factor type I.

myoblasts exposed to hydrogen peroxide (Chodkowska et al., 2018) and rats fed a high-fat diet (Melo et al., 2017; Salazar-López et al., 2017). Using high fat diet-induced obese mice, Naowaboot et al. (2018) observed that dietary FA reduces lipid synthesis and stimulates lipolysis to counteract dyslipidemia by exercing an anti-insulin resistance effect. In contrast, no change was observed in serum triglycerides or cholesterol concentrations when fattening lambs received free FA supplementation (Macías-Cruz et al., 2014; Valadez-García, 2019; Wang, Wang, et al., 2019), while FA-fed pigs (Li et al., 2015) and steers (González-Ríos et al., 2016) showed decreased meat lipid peroxidation rates. These findings suggest that FA modulates lipid metabolism only in presence of dyslipidemia. Overall, FA seems to act as a modulator of energy metabolism in animals with carbohydrate and lipid metabolic disorders.

Concerning protein metabolism, the information available to date is limited to sheep under different climatic conditions. While this phenol does not affect serum concentrations of total protein and urea in hair ewe lambs experiencing heat stress or thermoneutral conditions (Macías-Cruz et al, 2014, 2018; Valadez-García et al., 2019), in cold stressed-male lambs it caused an increase in serum total protein concentration (Wang, Wang, et al., 2019). In lambs fed feruloyl oligosaccharides, an increase in serum total protein concentrations has also been evident (Wang, Meng, et al., 2019). Both studies explained that FA increases total protein in blood because improves microbial protein synthesis and/or enzymatic antioxidant activity preventing protein oxidation (Wang et al., 2019 ab). In consequence, FA might stimulate protein synthesis and reducing its catabolism (cytoprotective effect) in order to improve protein metabolism, at least in ruminants. This beneficial effect of FA on protein metabolism requires further study to accurately understand the mechanism of action in ruminants and other production animals.

6. Ferulic acid in animal production

6.1. Effects on meat production

The meat industry demands new technologies to produce healthy animals with high average daily gain (ADG), feed efficiency, and muscle mass deposition without provoking detrimental effects on meat quality. On the contrary, a meat with improved organoleptic properties, such as appearance, flavor and tenderness, and extended shelf life is desirable. In this regard, feeding feedlot animals with FA is a current nutritional technology that produces *ante-* and *postmortem* benefits in ruminants and monogastric animals (Table 2). Although, the beneficial effects of this phenol on meat production have not been entirely consistent throughout published studies, which has been related to differences in factors such as specie, breed, sex, physiological state, oxidative status, dosage, and supplementation period (González-Ríos et al., 2016; Peña-Torres et al., 2019; Soberon, Cherney, & Cherney, 2012; Wang, Wang, et al., 2019). The main results reported for each species are described below.

6.1.1. Cattle

Most studies have reported no change for feedlot performance in FA-

Table 2
Effects of ferulic acid (FA) or derivates on feedlot performance, carcass characteristics and meat quality in ruminants and non-ruminants.

Animals	Dose/Period	Feedlot performance	Carcass traits	Meat quality (muscle *Longissimus thoracis*)	Reference
Heifers 3/4 *Bos Taurus*	0, 250 or 500 mg of FA kg^{-1} feed during 30 d	↑ Final BW and ADG, but DMI and feed efficiency unaffected	↑ HCW, CCW, carcass dressing, and MLT area, but fat thickness and marbling unaffected	Color, pH value, WBSF, cooking loss, WHC and sensory traits unaffected	Peña-Torres et al. (2021)
Crossbred steers 3/4 *Bos Taurus*	6 mg of FA kg^{-1} BW during 30 (FA30) or 60 (FA60) d	Final BW unaffected	-	Physicochemical and sensory traits unaffected. FA30: delayed lipid peroxidation FA60: ↑ ∑ PUFAs	González-Ríos et al. (2016)
Heifers and steers *Bos Taurus*	7 ppm of FA kg^{-1} BW during 56 d	ADG, DMI and feed efficiency unaffected	-	-	Flores-Campos et al. (2015)
Crossbred steers 3/4 *Bos Taurus*	240 ppm of FA/d during 30 or 60 d	Final BW unaffected	HCW, CCW, fat thickness, and MLT area unaffected	physicochemical and sensory traits unaffected	González-Ríos et al. (2013)
Dorset x Finn lambs	3, 6, and 9 g of FA/d during 5 d	↑ Feed intake and ADG unaffected with 3 and 6 g	-	-	Soberon, Cherney, and Cherney (2012)
Dorper x Pelibuey ewe lambs	300 mg of FA/d during 34 d	DMI, ADG, and feed efficiency unaffected	↑ Leg yield, without affecting other wholesale yields	-	Macías-Cruz et al. (2014)
Male hair lambs	300 and 600 mg/d	-	-	↑ Area and diameter of oxidative fibers Unaffected color and WBSF	Peña et al. (2018)
Dorper x Han cold-stressed lambs	80, 400, and 2000 mg of FA kg^{-1} feed during 30 d	↑ ADG and feed efficiency only with 80 mg. DMI and BW unaffected	-	-	Wang, Wang, et al. (2019)
Dorper x Han heat-stressed lambs	50, 100, 200, and 400 mg of FOs kg^{-1} feed	↑ ADG and feed efficiency, but DMI and BW unaffected	-	-	Wang, Meng, et al. (2019)
Katahdin x Dorper heat-stressed ewe lambs	250 mg of FA kg^{-1} feed during 40 d	↑ ADG and feed efficiency when Te > 35 °C, without affecting final BW	↑ Forequarter wholesale cut yields ↓ Hindquarter wholesale cut yields	pH, color, and WBSF unaffected	Valadez-García et al. (2021)
Weaned piglets DLY	0.05 and 0.45% of FA inclusion in the diet	Final BW, ADG, DMI, and feed efficiency unaffected	-	↑ proportion oxidative-glycolytic muscle fibers and improved mitochondrial function	Wang et al. (2021)
Landrace x Yorkshire pigs	25 ppm of FA kg^{-1} feed during 27 d	↑ ADG and final BW, but DMI and feed efficiency unaffected	↑ MLT area ↓ Fat thickness	↑ MDA ↓ Redness, flavor intensity, and WBSF	González-Noriega (2016)
Finishing pigs DLY	15 ppm of FA kg^{-1} feed	↑ ADG ↓ Feed conversion	↓ Fat thickness		Herrera et al. (2011)
Barrows DLY	100 mg of FA kg^{-1} feed during 28 d	-	Lean percentage, MLT area, and fat thickness unaffected	↓ MDA and WBSF, but color and ultimate pH unaffected	Li et al. (2015)

BW = body weight; ADG = average daily gain; DMI = dry matter intake; HCW = hot carcass weight; CCW = cold carcass weight; MLT = muscle *Longissimus thoracic*; WBSF= Warner-Bratzler shear force; WHC = water holding capacity; PUFAs = polyunsaturated fatty acids; n6 = omega-6 fatty acids; MDA = malondialdehyde; FOs = feruloyl oligosaccharides; Te = ambient temperature; DLY = terminal breeding Duroc x Landrace x Yorkshire.

fed cattle (Flores-Campos et al., 2015; González-Ríos et al., 2013, 2016). Although, Peña-Torres et al. (2021) observed an increase in final BW and ADG, as well as a trend to increase feed efficiency without altering dry matter intake (DMI) due to free FA supplementation in beef heifers exposed to high environmental temperatures; these beneficial effects were more evident with increasing doses of FA (0, 250 and 500 mg kg^{-1} feed). In carcass characteristics, this phenol compound has been shown to improve carcass yield without affecting any other trait in steers fed 240 ppm of FA d^{-1} for 30 or 60 d (González-Ríos et al., 2013), as well as carcass weight and yield, and LTM area in heifers fed 250 mg of FA kg^{-1} feed but not with a dose of 500 mg kg^{-1} feed (Peña-Torres et al., 2021). All those studies indicate that FA acted as growth promoter similar to β_2-AA to trigger a greater muscle mass deposition, and consequently, improved growth performance and carcass weight in beef cattle. As mentioned above, there is no sufficient evidence in the literature indicating that FA functions as β-AA, so other mechanisms of action could explain those beneficial effects; perhaps its antioxidant action is responsible given that the growing beef cattle experiences high metabolic rate and oxidative stress (Celi, 2011). Also, its antimicrobial mechanism of action in the modulation of ruminal fermentation could be considered.

Moreover, the dietary inclusion of free FA does not seem to affect physicochemical and sensory attributes of beef (González-Ríos et al., 2013, 2016; Peña-Torres et al., 2021). In fact, ultimate pH, color parameters, shear force, water holding capacity, cooking loss, intramuscular fat, and sensory traits (i.e., appearance, flavor, juiciness, and tenderness) were maintained within normal values in FA-supplemented cattle (Peña-Torres et al., 2021). Satisfactorily, as a result of the antioxidant activity, FA decreases malondialdehyde and metmyoglobin concentrations but also increases the amount of polyunsaturated fatty acids (PUFAs) in meat (González-Ríos et al., 2016). From a biological point of view, the increase in PUFAs is favorable for the cellular and metabolic functions during the animal's growth, and consumer health (Sioen et al., 2017). Overall, FA contributes to the reduction of meat damage and the increase of its shelf life because it minimizes lipid and protein oxidation. In addition, this phenol helps to produce healthier meat for human consumption by modifying the lipid profile.

6.1.2. Sheep

The beneficial effects of FA supplementation on sheep meat production are controversial and possibly depend on the presence of high oxidative stress (Valadez-García et al., 2021; Wang et al., 2019 ab). Thus, there was no effect of dietary supplementation of free FA on growth performance, and carcass traits in Dorset x Finn (Soberon, Cherney, & Cherney, 2012) and Dorper x Pelibuey (Macías-Cruz et al., 2014) lambs finished under a thermoneutral environment. These results were associated with adequate pro-oxidant: antioxidant balance of the animals, and this prevented a cytoprotective action by feeding FA. On the contrary, FA-fed lambs that developed high oxidative stress due to temperatures below zero (Wang, Wang, et al., 2019) or higher than 35 °C (Valadez-García et al., 2021) had higher ADG and feed efficiency than control lambs by increasing antioxidant enzymatic activity and decreasing lipid and protein oxidation. In agreement with this finding, Wang, Meng, et al. (2019) reported similar results with feruloyl oligosaccharides in a dose-dependent manner when lambs were exposed to moderate heat stress. Peña et al. (2018) also observed an increase in the cross sectional area of oxidative fibers without altering color parameters and shear force due to FA in sheep. Similarly, in heat-stressed ewe lambs fed FA, bib_Peña_Torres_et_al_2021Valadez-García et al. (2021) reported better yields in some wholesale cuts where oxidative fibers predominated, with no change in LTM meat quality. Overall, these findings show that FA improves feedlot performance only when lambs exhibit oxidative stress, which may be associated with a better antioxidant status and development of type I muscle fibers.

6.1.3. Pigs

Supplemental FA improves pig feedlot performance and some carcass characteristics, although the mechanism of action leading to these beneficial effects is unclear. In finished Landrace x Yorkshire pigs, supplementation of 15–25 ppm of FA kg^{-1} feed increased ADG, feed efficiency, final BW, and LTM area while decreasing fat thickness (González-Noriega, 2016; Herrera et al., 2011). As in cattle, the authors attributed these responses to a possible β-AA action of FA given that the antioxidant capacity of pigs was not affected. On the contrary, another study reported higher antioxidant capacity in the liver and LTM tissue without changes in back fat, lean percentage, and LTM area for FA-fed finishing pigs (100 ppm kg^{-1} feed; Li et al., 2015). Weaned pigs also did not respond to FA supplementation, as their feedlot performance did not change (Wang et al., 2021).

Results published so far suggest that the impact of FA on meat physicochemical characteristics and sensorial analysis depends on the dose administered, so that high doses are those that enhance these attributes of pork (Li et al., 2015). While the supplementation of 25 ppm of FA kg^{-1} feed promoted lipid peroxidation (González-Noriega, 2016), the feeding with 100 ppm of FA kg^{-1} feed decreased lipid oxidation in LTM (Li et al., 2015). Thus, high lipid peroxidation in meat caused a reduction in shelf life and a negative consumer perception regarding appearance and flavor (González-Noriega, 2016). On the contrary, low lipid oxidation had beneficial effects in pork, mainly improving tenderness and having a better red color (Li et al., 2015). As already indicated for other species, further studies are required to elucidate both mechanism of action and supplementation dose.

6.2. Effects on reproduction

The cyclical follicular production of ROS is essential for correct gonadal function, as they are necessary to produce energy and induce the ovulatory process (Kala, Shaikh, & Nivsarkar, 2017). On the other hand, elevated follicular ROS synthesis leads to oxidative stress, autoimmune premature ovarian failure and infertility in females (Mbemya, Vieira, Canafístula, Pessoa, & Ribeiro, 2017). In consequence, the exogenous supply of antioxidant compounds is a beneficial strategy to improve oxidative state and reproductive performance. The FA could promote better reproductive activity in farm animals due to its antioxidant activity (Tanihara et al., 2018), metabolic effect (de Oliveira Silva & Batista, 2017) and affinity for estrogen receptors (Kiyama, 2019; Table 3).

In prepubertal hair ewes, the dietary addition of free FA stimulated the reproductive tract development, follicular growth, and ovulation during the natural anestrus season (Macías-Cruz et al., 2018). The authors concluded that FA shortens puberty age and accelerates sexual maturity in lambs born in autumn. Similar results were reported in mice fed an extract rich in FA and in their offspring; additionally, higher estrogens and progesterone production was also observed in that study, with no change in luteinizing hormone and follicle stimulating hormone concentrations (Moshfegh et al., 2016). Heifers fed FA also show no change in the secretory activity of adenohypophysis gonadotropic cells (Gorewit, 1983). Therefore, these overall results seem to indicate that the reproductive benefits of this phytochemical are associated with a direct action at the ovary level. On the other hand, under *in vitro* conditions, gametes can experience cell damage from increased ROS production when exposed to atmospheric oxygen and a medium without antioxidant defense (Frankel, 2012, pp. 209–258). *In vitro* studies with prepubertal sow oocytes show that FA favors oocyte maturation and fertilization, and embryonic development due to its antioxidant function, specifically activating the Nrf2/ARE pathway (Lee & Hyun, 2017; Tanihara et al., 2018).

In addition to its antioxidant effect, FA modulates the ovarian endocrine function in the following ways: 1) its high affinity to estrogen receptors (Kiyama, 2019), 2) its pro-insulin action regulating the insulin-glucose system (de Oliveira Silva & Batista, 2017; Macías-Cruz

Table 3
Effect of ferulic acid (FA) or derivates on animal reproduction.

Animal/Cells	Dose	Response	Reference
Prepubertal hair ewes	300 mg of FA	↑ Peso del tracto reproductivo ↑ Masa y actividad ovárica ↓ Concentración sérica de glucosa	Macías-Cruz et al. (2018)
Holstein heifers	100 and 500 mg of FA	↑ GH FA did not affect LH concentration	Gorewit (1983)
Female Balb/C mice	100 and 200 mg of date palm pollen rich in FA	↑ Size and ovarian activity of mothers and their offspring ↑ E_2 and P_4 ↑ Embryonic development	Moshfegh et al. (2016)
Sow oocytes	10 μM of FA	↑ *In vitro* maturation, fertilization and blastocyst formation rate.	Lee and Hyun (2017)
Sow oocytes during *in vitro* maturation	5 μM, 10 μM, and 20 μM of FA	↑ GSH (5 μM) ↑ Blastocyst formation (10 μM) ↓ Intracellular ROS (20 μM)	Tanihara et al. (2018)
Lambs with scrotal heat stress	33 mg of γ-oryzanol kg^{-1} metabolic weight	↓ ROS in testicles ↑ Sperm motility FA did not affect MDA, amount of parenchyma, or plasma testosterone concentration	Escobar et al. (2019)
Mice with lead poisoning	50 mg of FA kg^{-1} BW	↓ MDA and ↑ GSH and TAC ↑ Number of germ and somatic cells in testis ↑ Testosterone and sperm quality	Hasanein et al. (2018)
Rats exposed to gamma radiation	50 mg of FA kg^{-1} BW	↓ MDA and ↑ catalase activity ↑ Testis size and testosterone concentration ↓ Sperm abnormalities	Gawish et al. (2016)
Rats with induced diabetes	50 mg of FA kg^{-1} BW	↑ Testis weight, testosterone concentration and sperm quality	Roy et al. (2014)
Thawed equine semen	165 μM of FA at a sperm concentration of 25 × 106 cells/mL	↑ Integrity of plasma and acrosomal membrane and↑ mitochondrial potential	Affonso et al. (2017)

GH = growth hormone; E2 = estrogens; P4 = progesterone; GSH = intracellular glutathione; ROS = reactive oxygen species; MDA = malondialdehyde; TAC = total antioxidant capacity.

et al., 2018), and 3) its ability to stimulate GH (Gorewit, 1983) and IGF-I (Chodkowska et al., 2018) release. The joint action of these mechanisms promotes a favorable metabolic environment in the ovaries to improve folliculogenesis and steroidogenesis, positively impacting follicular and luteal size, synthesis of steroidal hormone, and oocyte quality and maturation (Macías-Cruz et al., 2018; Moshfegh et al., 2016). High follicular and luteal endocrine activity due to FA helps the proper functioning of the hypothalamic-pituitary-gonadal axis (Tetaping et al., 2017).

In males, some benefits have also been reported due to FA. Rams with scrotal heat stress have reduced ROS levels and increased sperm motility without altering serum testosterone concentrations when fed a compound rich in FA (Escobar et al., 2019). In studies conducted in mice with testicular damage (Gawish et al., 2016; Ḥasanein et al., 2018) or diabetes (Roy et al., 2014), dietary FA reactivated endocrine and exocrine function of the testes. The cryopreservation of equine semen has also been favored with the addition of FA in the medium because it maintains mitochondrial, acrosomal, and plasma membrane stability (Affonso et al., 2017).

7. Restrictions

In contrast to the aforementioned benefits, improper use of FA can also have negative effects. Different studies have shown that high-dose supplementation in lambs (>2000 mg of FA kg^{-1} feed) or prolonged use in cattle (60 d) decreases nutrient digestibility (Wang, Wang, et al., 2019) or exerts pro-oxidant activity (González-Ríos et al., 2016), respectively. The first has been associated with the antibacterial action exerted by phenolic compounds on cellulolytic bacteria such as *Ruminococcus albus* and *R. flavefaciens* (Vasta et al., 2019). So, by reducing the availability of nutrients, productive benefits in feedlot and carcass may not be attained (Flores-Campos et al., 2015; González-Ríos et al., 2016; Macías-Cruz et al., 2014; Peña-Torres et al., 2021; Soberon, Cherney, & Cherney, 2012). On the other hand, the excessive accumulation of this phenol in tissues causes an increase in the iron reduction capacity and, consequently, oxidative damage (Maurya & Devasagayam, 2010). Some studies have shown FA pro-oxidant activity in muscle, affecting negatively both quality and shelf life of the meat (González-Noriega, 2016; González-Ríos et al., 2016). Therefore, research is required to establish the specific doses for each species to avoid adverse effects from the use of FA.

8. Future prospects of ferulic acid in meat production

Based on mechanisms of action, and productive and reproductive effects, new possible applications of FA in the meat production chain could be suggested, but all must be previously validated. At first, supplemental FA could increase availability of animals for fattening, and its growth potential. In this sense, FA may be a viable option to ensure conception by enhancing natural and assisted reproduction programs. According to results in hair sheep and mice, FA stimulates sexual maturation (Macías-Cruz et al., 2018; Moshfegh et al., 2016) and improves gonads exocrine and endocrine function (Ḥasanein et al., 2018). If FA exerts these actions in breeds that present natural seasonal anestrus or in any farm animal species, it would be a promising natural alternative to induce early puberty and stimulate ovarian activity instead of synthetic hormones. In assisted reproduction, current information shows that FA is useful in artificial insemination and *in vitro* fertilization of sow oocytes due to its cytoprotective mechanisms (Affonso et al., 2017; Lee & Hyun, 2017; Tanihara et al., 2018); however, this needs to be tested on different species. During pregnancy, FA supplementation may be a strategy to improve fetal programming of muscle and gonads, and this could have long-term beneficial effects on the postnatal growth and development of the offspring. In murine models, FA stimulates differentiation of myoblasts to oxidative muscle fibers (Chen et al., 2019) and increases the number of follicles and corpus luteum in offspring (Moshfegh et al., 2016).

Feeding with FA may modulate the farm animals' growth during the fattening under adverse conditions. In ruminants, it has an antioxidant action that increases feed efficiency and weight gain in presence of oxidative stress associated with thermal stress (Wang et al., 2019 ab; Valadez-García et al., 2021). Considering the current problem of global warming, this is a finding of particular interest since the supplementation of this natural antioxidant in animals exposed to extreme environmental temperatures may be a strategy to guarantee meat production in the context of climate change.

On the other hand, there is concern about the increasing antimicrobial resistance in livestock and that such resistance may be transmitted to humans; so, an alternative to the use of antibiotics in farm animals should be found (Clifford et al., 2018). Studies on bacterial cultures show that FA may modulate GIT microbiota (Gong et al., 2019)

and has bactericidal action on some of the main zoonotic bacteria that cause several diseases in farm animals (Borges et al., 2013). Therefore, its activity as an eubiotic agent (Marquardt & Li, 2018) and *in vivo* therapeutic potential should be tested. Another possible antimicrobial application of this phenol may be its use as a preservative for meat since it inhibits bacterial biofilm formation in surfaces (Borges, Saavedra, & Simoes, 2012).

Finally, given that FA counteracts dyslipidemia (Salazar-López et al., 2017) and improves insulin sensitivity in muscle (Chodkowska et al., 2018), it can be an alternative to treat obesity in farm animals and insulin resistance in offspring born from dams subjected to nutritional restriction during the pregnancy. Underfed dams during pregnancy is a common issue in livestock systems with negative implications for offspring's postnatal metabolism and growth (Du, Wang, Fu, Yang, & Zhu, 2015). The main adverse effects are decreased myogenesis during the embryonic stage and lower muscle development, higher fat deposition, and peripheral insulin resistance in postnatal life (Khanal & Nielsen, 2017). The excessive accumulation of adipose tissue causes detrimental effects on meat quality in young animals (Corazzin, Bianco, Bovolenta, & Piasentier, 2019, pp. 119–165) and reproductive failure in adults (Khanal & Nielsen, 2017).

9. Conclusions

According to current information, FA can increase animal protein production by improving the productive and reproductive performance of farm animals. However, information remains scarce, leading to open an extensive field of research on the application of this phytochemical. Environmental conditions, species, oxidative state of the animal, bioavailability, mechanisms of action, and dosage of the product, are factors that should be considered in future research. Together, the information available to date and subsequent studies will allow the establishment of management strategies that make this natural compound a promising option to guarantee food safety without harming animal welfare and human health.

Credit author statement

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Free ferulic acid supplementation of heat-stressed hair ewe lambs: Oxidative status, feedlot performance, carcass traits and meat quality

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ABSTRACT

Twenty-two Katahdin × Dorper ewe lambs (average weight = 23.5 ± 2.8 kg) were individually housed during a 40-d feeding study and then slaughtered to evaluate effects of free ferulic acid (FA; 0 and 250 mg/kg of feed) on oxidative status, feedlot growth, carcass and non-carcass traits, wholesale cut yields and meat quality under heat stress conditions. Overall feeding FA decreased protein oxidation without affecting oxidative stress index, while growth rate and feed efficiency increased only in the hottest period (i.e., 28 to 45 °C). The FA supplementation increased kidney-pelvic-heart and mesenteric fat deposition, as well as yields of forequarter, shoulder, ribs, loin, and breast and flank, but decreased yields of hindquarter, neck, plain loin and leg. Carcass characteristics and meat quality were unaffected by FA. Overall, FA supplementation of heat-stressed hair ewe lambs enhanced feedlot performance under extreme heat stress and increased internal fat reserves, while changing muscle mass deposition, possibly because it prevented protein oxidation.

1. Introduction

Hair sheep are widely distributed in arid, semi-arid and tropical regions, where their productivity is compromised during hot summers (Sejian et al., 2017). When hair sheep breeds are exposed to an ambient temperature > 30 °C, they begin to suffer heat stress (HS; Vicente Pérez et al., 2020), which causes the sheep to activate physiological, metabolic, endocrine, and cellular mechanisms to thermoregulate. Although such mechanisms are effective in restoring normothermia in hair sheep breeds, they also increase maintenance energy needs (Macías-Cruz et al., 2013, 2020) and cause high oxidative stress (Belhadj, Chniter, Najar, & Ghram, 2019). As a consequence, heat-stressed hair lambs decrease their average daily gain (ADG), feed efficiency, cold carcass weight (CCW) and loin yield, as well as produce slightly tougher meat associated with its high ultimate pH and low water holding capacity (Macías-Cruz et al., 2013, 2020).

Use of natural antioxidants can be a useful strategy to mitigate HS effects on meat production of hair sheep. Some authors have stated that plant extracts with antioxidant actions enhance growth performance, carcass traits and meat quality in heat-stressed wool lambs. In a hot summer study, the naringin flavonoid increased ADG and feed efficiency in Awassi lambs (Alhidary & Abdelrahman, 2016), while the lycopene carotenoid improved hot carcass weight (HCW) in Bamei lambs (Jiang et al., 2015). Similarly, heat-stressed Ujumqin lambs fed chestnut tannins had enhanced growth performance, while lipid and myoglobin oxidation in skeletal muscle was prevented (Liu, Li, Mingbin, Zhao, & Xiong, 2016). However, there are no previous reports on use of any natural antioxidant under hyperthermia conditions in fattening hair lambs.

Ferulic acid (FA) is a phenolic compound that has received attention in the livestock sector because of its antioxidant properties. This phenolic compound scavenges free radicals and induces expression of antioxidant enzymes by activating the nuclear factor E2-related factor 2/antioxidant element response pathway (Nrf2/ARE; Ghosh, Basak, Dutta, Chowdhury, & Sil, 2017). Associated with these mechanisms, FA can improve physiological and metabolic processes, and therefore, animal growth (González-Rios et al., 2016; Wang, Wang, et al., 2019). In thermoneutral conditions, FA decreased shear force of finishing pig meat

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(Li et al., 2015) while, in cattle, it delayed meat lipid peroxidation with the resultant longer storage stability (González-Ríos et al., 2016). In contrast, FA in sheep did not affect feedlot performance and carcass characteristics under optimal ambient temperatures (Macías-Cruz et al., 2014; Soberon, Cherney, & Cherney, 2012), whereas in cold stressed lambs (Wang, Wang, et al., 2019), it increased ADG and feed efficiency by enhancing oxidative status. This suggests that, in fattening lambs, FA has greater effects only in association with the presence of high oxidative stress. However, this has not been demonstrated in heat-stressed lambs of any breed.

This study was designed to test the hypothesis that FA enhances productive performance, carcass characteristics, wholesale cut yields and meat quality in heat-stressed hair ewe lambs by improving oxidative status. Thus, the objective was to evaluate effects of dietary supplementation of free FA on oxidative status markers, feedlot performance, carcass and non-carcass traits, wholesale cut yields, and meat quality in heat-stressed ewe lambs.

2. Materials and methods

2.1. Study site

The study was carried out during summer (i.e., August and September) at the Sheep Experimental Unit and Meat Laboratory of the Instituto de Ciencias Agrícolas (ICA), Universidad Autónoma de Baja California (UABC). The ICA-UABC is located in the Mexicali Valley, Baja California, northwestern México (32° 24′ N and 115° 11′ W), where the climate is arid and dry, with extreme temperatures in summer (>40 °C) and winter (<0 °C). In this region, rainfall is low (85 mm/year) and occurs mainly during winter (INEGI, 2017).

2.2. Animals, management and treatments

All experimental procedures of management and slaughter of lambs were according to FASS guidelines (FASS, 2010) and Mexican Official Norms: NOM-062-ZOO-1999, Technical specifications for the production, care and use of laboratory animals; NOM-051-ZOO-1995, Humanitarian treatment in animal mobilization; and NOM-033-SAG/ZOO-2014, Humanitarian slaughter of domestic and wild animals.

Twenty-two Katahdin × Dorper ewe lambs with initial body weight (BW) of 23.5 ± 2.8 kg and aged 4 months were used in a 55-d feeding study (15 d for adaptation and 40 d for feedlot evaluation). During the adaptation period, all lambs were adapted to individual pens and basal diet, with concomitant sanitary management of a single subcutaneous administration of 0.2 mg/kg BW of ivermectin (Iverfull; Aranda Laboratory, Mexico City, Mexico), and intramuscular administration of 250,000 IU of vitamin A, 37,500 IU of vitamin D and 25 mg of vitamin E (Vigantol ADE strong; Bayer Laboratory, Mexico City, Mexico). The individual pens had an area of 1.5 m^2, cyclonic mesh walls, dirt floor, galvanized sheet metal shade (2.5 m height), and a bucket for diet and another for water. The basal diet was formulated to meet nutritional requirements for fattening lambs in the finishing phase (11.7 MJ metabolizable energy [ME]/kg dry matter [DM] and 16% crude protein [CP]) (NRC, 2007).

After the adaptation period, the initial BW of each lamb was recorded to create pairs of similar BW as a blocking factor. Ewe lambs of each pair were randomly assigned to one of the two dietary treatments ($n = 11$): basal diet with 0 (control) or 250 mg of FA/kg of feed. The FA dosage was determined according to a previous study (González-Ríos, Gil, & Berrondo, 2013), where a dosage of 250 mg/kg of diet was recommended for finishing cattle. To ensure optimal FA intake, all ewe lambs were weighed individually every 10 d to calculate daily feed intake (BW*0.04), and consequently expected daily FA intake. Therefore, the daily amount of FA fed per lamb was based on expected daily feed intake, which was 235, 258, 275, and 295 mg during days 1 to 10, 11 to 20, 21 to 30 and 31 to 40, respectively, of the feeding period. The FA was mixed with ground wheat grain to create the FA dose of 250 mg into 30 g of mixture, so that the mixture amount that contained the expected daily FA intake per lamb female was weighed and offered daily before the morning feeding. In the control group, 30 g of ground wheat grain was offered as placebo before the morning feeding. Treatments were offered during the 40-d feedlot evaluation period.

The diet was offered twice (0600 and 1800 h) and the water three times a day (0600, 1200 and 1800 h) to guarantee ad libitum access. Diet samples were collected weekly, dried in forced-air oven at 60 °C for 24 h, milled through a 2-mm screen (Wiley mill model 4; Thomas Scientific, Swedesboro, NJ, USA) and mixed to obtain two subsamples, which were used for chemical analyses (AOAC, 1990; Van Soest, Robertson, & Lewis, 1991). The ME was calculated according to NRC (1985). Ingredients and chemical composition of the diet are shown in Table 1. Health status of the lambs was monitored daily by direct visualization, and none showed signs of disease during the study.

2.3. Climatic conditions and physiological variables

Daily climatic conditions were measured with a thermohygrometer (Thermotracker, Higro, Culiacán, Sinaloa, Mexico) placed in the middle of the study area at a height similar to that of the lambs' heads and programmed to record temperature (Te) and relative humidity (RH) every 20 min. The temperature-humidity index (THI) was obtained using the formula (LPHSI, 1990) modified by Marai, El-Darawany, Fadiel, and Abdel-Hafez (2007): $THI = Ta - [(0.31 - (0.31 * HR)) * (Ta - 14.4)]$. In all climatic variables, daily average, maximum and minimum values were calculated for 10-d periods and overall. Additionally, averages per hour were estimated.

Rectal temperature (RT) and respiratory rate (RR) were measured at 0600 and 1800 h on days 1, 10, 20, 30 and 40 of the feeding period. The RR was quantified by counting the number of intercostal movements by 30 s, multiplied by two to obtain the number of breaths per minute (bpm). The RT was obtained by inserting a digital thermometer (Delta Track, Pleasanton, CA, USA) rectally until the temperature remained constant for at least 30 s.

2.4. Serum oxidative status markers

On days 1, 20 and 40, the serum concentrations of malondialdehyde (MDA), advanced oxidation protein products (AOPP), total oxidant capacity (TOC), total antioxidant capacity (TAC) and oxidative stress index (OSI) were measured. Blood samples were collected at 0600 h (before the morning feeding) from the jugular vein into 6-mL vacutainer tubes, which were centrifuged at 3500 × g for 15 min at 10 °C. Serum was stored in duplicate in 2-mL vial at −20 °C until analysis. Oxidative

Table 1
Ingredients and chemical composition of the basal diet.

Ingredient composition (% mixed basis)	
Alfalfa, hay	10
Wheat, straw	15
Wheat, grain ground	62
Soybean, meal	11
Premix, mineral/vitamin	0.5
Limestone	0.5
Dicalcium phosphate	0.5
Salt	0.5
Chemical composition (DM basis)	
Dry matter (%)[a]	90.5
Crude protein (%)	16.1
Ether extract (%)	3.5
Ash (%)	7.8
Acid detergent fiber (%)	18.0
Neutral detergent fiber (%)	25.7
Metabolizable energy (MJ/kg)[b]	12.4

[a] Only dry matter (DM) was calculated in mixed basis.
[b] Calculated using formulas from NRC (1985).

markers were quantified with a microplate spectrophotometer (Bio-Tek Instruments, Inc., Winooski, VT, USA), according to the methodologies: *N*-methyl-2-phenyl-indole method for MDA (Witko-Sarsat et al., 1998), chloramine-T method for AOPP (Witko-Sarsat et al., 1996), o-dianisidine (3,3′-dimethoxybenzidine) method for COT (Erel, 2005), and ABTS radical cation method for CAT (Erel, 2004). The OSI was estimated using the TOC/TAC ratio (Karaagac, Tekin, Koruk, & Aksoy, 2011).

2.5. Feedlot performance

Individual BW was recorded every 10 d before the morning feeding. The amounts of feed and water offered and refused were recorded by lamb daily. From this data, ADG, total BW gain, DM intake, feed efficiency and daily water intake were calculated for 10-d periods (1 to 10, 11 to 20, 21 to 30 and 31 to 40 d) and for the overall period (1 to 40 d). Both initial and final BW were also considered.

2.6. Carcass characteristics and non-carcass components

Once the feedlot phase was completed, lambs were fasted for 12 h and then transported to the Meat Laboratory for slaughter by the exsanguination method described in the Official Mexican Standard NOM-033-SAG/ZOO-2014. All lambs were bled, skinned and eviscerated to measure individual HCW and weights of non-carcass components such as blood, skin, head, feet, full and empty gastrointestinal tract, heart, liver, spleen, kidneys, pelvic-renal-heart fat (KPH), and omental and mesenteric fat. Carcasses were chilled at 4 °C for 24 h to obtain CCW, conformation (scale from 1 = bad to 8 = excellent; Smith, Griffin, & Kenneth, 2001) and morphometric measurements as carcass length, thorax depth, leg length, and leg perimeter (Parés-Casanova, 2013). Subsequently, carcasses were ribbed along the midline, and the right half was ribbed again between the 12th and 13th rib to facilitate measure of *Longissimus thoracis* (LT) muscle area (dot square grid of 64 mm^2) and fat thickness (vernier caliper). Hot and cold carcass yields were calculated expressing the HCW and CCW as a percentage of the empty BW (EBW = slaughter BW − [full − empty gastrointestinal tract]). The KPH fat weight was expressed as a percentage of the HCW, and the rest of the non-carcass component weights were expressed as percentages of the EBW.

2.7. Wholesale cut yields

The right half carcass was weighed and sectioned according to Avendaño-Reyes et al. (2011) into the cuts: forequarter, hindquarter, neck, loin, ribs, shoulder, plain loin, leg, and breast and flank. The weight of each cut was expressed as a percentage of the half carcass weight to obtain yield.

2.8. Meat quality evaluation

The LT muscle was used to evaluate meat quality traits (i.e., pH, color and shear force). At 45 min and 24 h *postmortem*, a portable pH meter provided with a penetration electrode (Hanna Instruments, model HI 98140, Woonsocket, RI, USA) was used to measure pH in the carcass loins at the height of the 12th and 13th rib where the LT is located. The loin wholesale cut (loin of the 4th to 12th ribs) contained the LT muscle, so it was dissected after its weight was recorded. The LT muscle was vacuum packaged, aged (14 d at 4 °C) and finally unpacked for blooming. Five grams of muscle sample were separated within the first minute of blooming to determine storage pH, likewise a steak to measure shear force. The meat sample was liquefied with 25 mL of distilled water and the storage pH was measured directly in the mixture with a benchtop pH meter (Model HI-2210, Hanna Instruments Digital, Woonsocket, RI). For shear force, steaks were cooked until an internal temperature of 71 °C (electric skillet, Cook Master Oster, model 3222-3, Mississauga, ON, Canada; Meat thermometer Hanna, model HI-93551, Woonsocket, RI, USA and then cooled at 25 to 30 °C) to cut 1.27 cm cubes on each side. Cooked meat cubes were sheared in longitudinal orientation to the muscle fibers with a Warner-Bratzler shear force device (Salter 235, Manhattan, KS, USA). The meat color was measured after 30 min of blooming. A colorimeter (Model CR-400, Konica Minolta Sensing, Inc., Osaka, Japan; D65 illuminator and 10° observer) was collocated on the surface of the meat to record lightness (L*), redness (a*), yellowness (b*), color saturation index (Chroma, C*) and Hue angle (H*). All meat quality measurements were made in triplicate for each lamb.

2.9. Statistical analysis

All statistical analyses were developed using the SAS program (SAS Inst. Inc., Cary, NC, USA). Climatic variables were analyzed with PROC MEANS to obtain values of descriptive statistics. The Shapiro-Wilk normality test was applied to all study variables using PROC UNIVARIATE. Data of ISO presented a non-normal distribution ($P > .05$), so they were transformed with the log function to obtain normality. Data of overall feedlot performance, carcass characteristics, non-carcass components, wholesale cut yields and meat quality were subjected to analysis of variance in a randomized complete block design (RCBD) using PROC MIXED. Physiological variables, feedlot performance by period and oxidative stress markers were also subjected to analysis of variance, but using a RCBD with repeated measures over time where the models included fixed effects of block, FA supplementation, time (sampling day or period) and the FA supplementation x time interaction. Different variance-covariance structures were verified to fit the model, and the compound symmetry structure showed the best fit according to criteria of lowest BIC and AIC values (Littell, Henry, & Ammerman, 1998). Treatment means were compared using LSMEANS/PDIFF to declare differences at $P \leq .05$ and trends at $0.05 < P \leq .10$. In the absence of interaction ($P > .05$), means by time were analyzed with orthogonal polynomials.

3. Results

3.1. Climatic conditions and physiological variables

Daily averages for Te, RH and THI were 33.41 ± 1.74 °C, 53.92 ± 8.07% and 30.37 ± 1.68 units, respectively. The hottest conditions occurred in the first 10 d (Te = 35.35 °C, RH = 55.74% and THI = 32.22 units) and were slightly lower during the last 30 d (Fig. 1). The Te remained above 30 °C from 0800 to 2200 h and THI above 22.2 units during the 24 h (Fig. 2), with average minimum and maximum values at 0600 (Te = 25.33 ± 3.07 °C and ITH = 24.57 ± 2.91 units) and at 1600 h (Te = 44.13 ± 2.44 °C and ITH = 37.36 ± 1.47 units). In the case of physiological variables, FA supplementation did not affect ($P \geq .30$) RR and RT in the morning or afternoon; however, the sampling day caused variation ($P < .01$) in them, since both variables had a quartic effect in the morning and a cubic effect in the afternoon as the feedlot days increased (Table 2).

3.2. Oxidative stress markers

The FA supplementation x sampling day interaction did not affect ($P \geq .18$) serum concentrations of any oxidative stress marker (Table 3). In general, supplemental FA tended ($P = .06$) to decrease serum AOPP concentration, without modifying ($P \geq .20$) serum levels of MDA, TOC, TAC and OSI. The MDA, TOC, and TAC decreased quadratically ($P < .01$), and AOPP and OSI decreased linearly ($P < .01$) with progression of the feeding period.

3.3. Feedlot performance

While FA supplementation did not alter ($P \geq .38$) overall feedlot

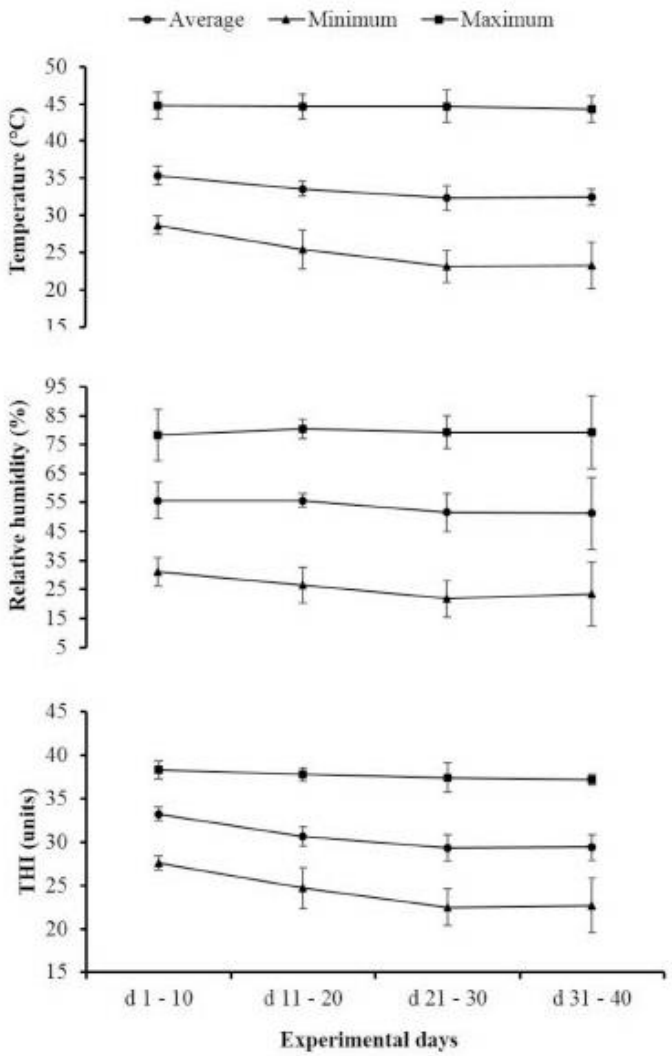

Fig. 1. Temperature, relative humidity, and temperature-humidity index (THI) for 10-d periods during the feedlot phase.

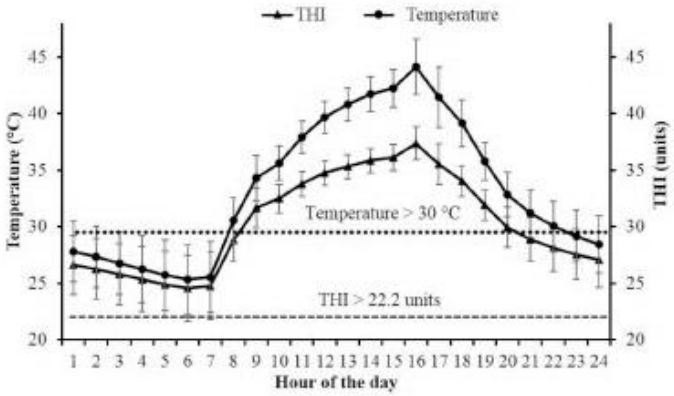

Fig. 2. Diurnal patterns for temperature (Te) and temperature-humidity index (THI) during the feedlot phase (mean ± SD). Non-continuous lines indicate the upper limit of Te (····) and THI (—) considered as thermoneutral.

Table 2
Effects of ferulic acid on rectal temperature and respiratory rate during sampling days in heat-stressed hair ewe lambs.

Items	Treatments (T)[a]			Sampling days (D)						P-Values		
	Control	FA	SEM	1	10	20	30	40	SEM	T	D	T × D
Respiratory rate (breaths per minute)												
0600 h[c]	107.31	108.40	2.16	86.82	106.64	105.73	117.55	122.55	2.70	0.73	<0.01	0.11
1800 h[b]	173.50	170.50	1.83	157.48	159.64	185.73	190.64	167.00	2.62	0.30	<0.01	0.59
Rectal temperature (°C)												
0600 h[c]	39.80	39.78	0.06	39.86	39.93	39.67	39.85	39.70	0.05	0.93	<0.01	0.01
1800 h[b]	40.18	40.17	0.09	40.24	40.12	40.23	40.28	40.01	0.06	0.91	<0.01	0.15

[a] Ewe lambs fed 0 or 250 mg of free ferulic acid (FA) per kg of diet.
[b] Cubic effect due to sampling day.
[c] Quartic effect due to sampling day.

Table 3
Effects of ferulic acid on serum oxidative stress markets during sampling days in heat-stressed hair ewe lambs.

Items[b]	Treatments (T)[a]			Sampling days (D)				P-Values		
	Control	FA	SEM	1	20	40	SEM	T	D	T × D
MDA (μmol/L)[d]	1.60	1.36	0.13	1.93	1.21	1.30	0.12	0.20	<0.01	0.49
AOPP (μmol/L)[c]	7.25	6.59	0.26	8.94	6.73	5.08	0.20	0.06	<0.01	0.70
TOC (μmol Eq H_2O_2/L)[d]	6.40	6.16	0.50	10.32	4.27	4.24	0.45	0.74	<0.01	0.53
TAC (μmol Eq Trolox/L)[d]	1.96	1.13	0.15	1.83	0.71	0.94	0.15	0.76	<0.01	0.49
OSI (arbitrary units)[c]	0.62	0.57	0.06	0.68	0.62	0.47	0.05	0.52	<0.01	0.18

[a] Ewe lambs fed 0 or 250 mg of free ferulic acid (FA) per kg of diet.
[b] MDA = Malondialdehyde, AOPP = Advanced oxidation protein products, TOC = Total oxidant capacity, TAC = Total antioxidant capacity, OSI = oxidative stress index.
[c] Linear effect due to sampling day.
[d] Quadratic effect due to sampling day.

performance (Table 4), the FA supplementation x period interaction affected ($P < .05$) productive variables, but not ($P \geq .15$) water intake (Fig. 3). During the first 10 d, there were higher ($P \leq .01$) ADG, total BW gain and feed efficiency due to FA feeding, without affecting ($P = .45$) DM intake. Between days 11 and 20, FA supplementation increased ($P = .05$) DM intake with no change ($P \geq .15$) of ADG, total BW gain and feed efficiency. However, in d 21 to 40, feedlot performance was unaffected ($P \geq .22$) by FA.

3.4. Carcass and non-carcass traits, wholesale cut yields and meat quality

Feeding FA increased ($P \leq .03$) KPH and mesenteric fat deposition, and tended ($P = .07$) to decrease leg perimeter, without affecting ($P \geq .11$) any other carcass characteristics or fat deposition (i.e., HCW, CCW, carcass yields, conformation, MLT area, carcass length, thorax depth, leg length, fat thickness and omental fat; Table 5). However FA supplementation increased ($P \leq .04$) yields of forequarter, shoulder, and breast and flank, as well as tending to increase loin ($P = .08$) and rib ($P = .10$) yields, but decreased ($P \leq .04$) yields of hindquarter, neck, plain loin and leg (Table 6). Non-carcass components (Table 7) and meat quality traits (Table 8) were unaffected ($P \geq .11$) by FA.

Table 4
Effects of ferulic acid on overall feedlot performance of heat-stressed hair ewe lambs.

Items	Treatments[a]		SEM	P-Values
	Control	FA		
Initial body weight (kg)	23.61	23.46	0.19	0.60
Final body weight (kg)	30.97	30.97	0.31	1.00
Total body weight gain (kg)	7.36	7.51	0.26	0.70
Daily weight gain (kg)	0.185	0.189	0.006	0.71
Dry matter intake (kg)	1.08	1.09	0.02	0.78
Feed efficiency (kg/kg)	0.170	0.175	0.005	0.39
Water intake (L/d)	4.78	5.09	0.24	0.38

[a] Ewe lambs fed 0 or 250 mg of free ferulic acid (FA) per kg of diet.

4. Discussion

4.1. Climatic conditions and physiological response

Ewe lambs were exposed to high environmental Te (33.4 °C), exceeding the upper limit of its thermoneutral zone (30 °C; Vicente-Pérez et al., 2020) and experiencing constant HS during the feedlot phase, which was extremely severe in terms of THI (THI ≥ 25.6 units; Marai et al., 2007). It is noticeable that overall environmental conditions were even hotter in the first 10 days of the study (Te = 35.3 °C and THI = 32.2 units) and then declined slightly the following 30 days (Te = 32.7 °C and THI = 29.7 units). As a result, the ewe lambs experienced hyperthermia most of the daytime because their evaporative heat losses were insufficient to dissipate accumulated heat load (RT = 40.2 °C and RR = 172 rpm). At dawn, there was slight thermal relief, since they had decreased their core temperature by 0.4 °C overmorning. That the free FA did not affect RT and RR in our ewe lambs is similar to results reported in heat-stressed wool sheep fed another natural antioxidant (Alhidary & Abdelrahman, 2016).

4.2. Oxidative stress

To our knowledge, this is the first study using free FA to improve the oxidative status in heat-stressed sheep. Inexplicably, results showed that this FA did not decrease the overall oxidative stress by increasing the TAC in hair ewe lambs suffering hyperthermia. Previous studies have reported better TAC and antioxidant enzyme activity in Dorper x Han lambs fed FA under cold stress (Wang, Wang, et al., 2019), as well as when they were fed feruloyl oligosaccharides (FA derivative) under moderate HS (Wang, Meng, et al., 2019). These beneficial effects occurred in a dose-dependent manner, with better responses at low dosages. Thus, we suggest that our oxidative state results may be associated with a long gap between FA feeding and sampling times because free FA is rapidly metabolized and excreted in ruminants about 4 to 5 h post-ingestion (Soberon et al., 2012), and blood samples were taken 24 h after the last FA ingestion. Future studies could be conducted to

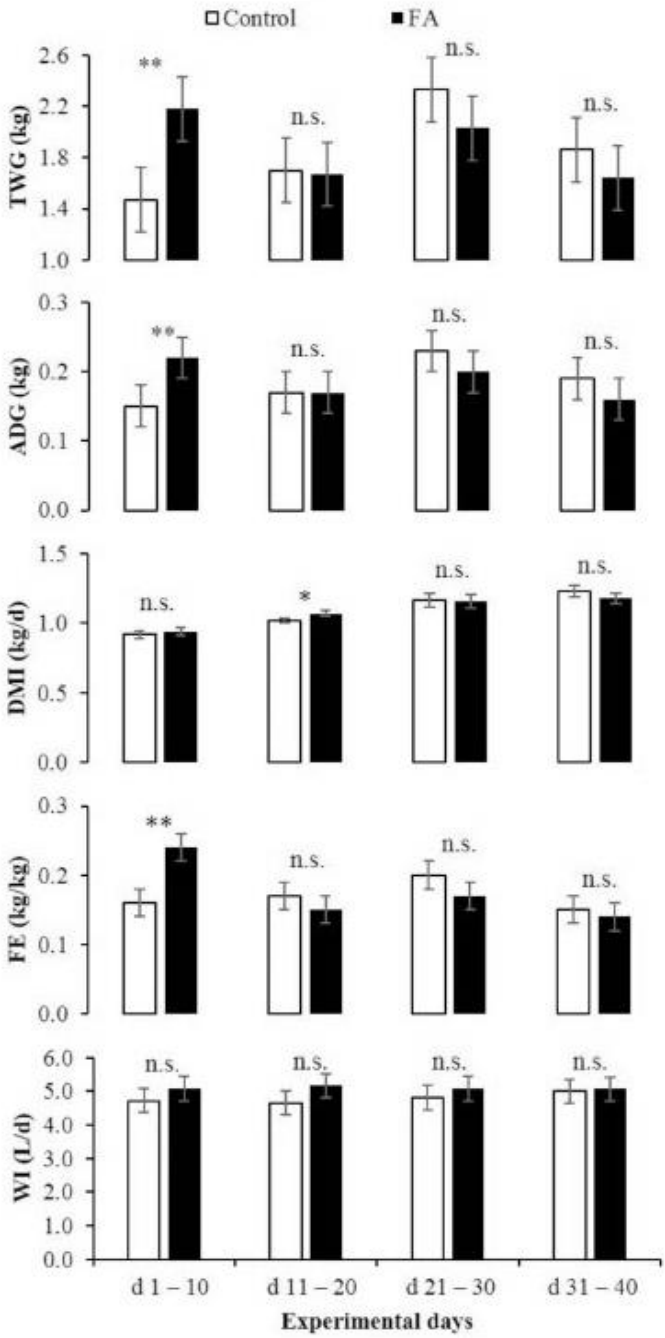

Fig. 8. Effects of ferulic acid (FA) on feedlot performance of heat-stressed hair ewe lambs by period [TWG = total body weight gain; ADG = average daily gain; DMI = dry matter intake; FE = feed efficiency; WI = water intake]. * $P < .05$, ** $P < .01$ and n.s. $P > .05$.

determine optimal dose and frequency of supplemental free FA for hair lambs fattened under HS and, if FA is offered in a single daily dose, it is recommended to measure oxidative stress markers before 5 h post-ingestion.

Interestingly, the supplemental FA was particularly effective in reducing protein oxidation (AOPP), but not lipid peroxidation (MDA), which could have beneficial implications to maintenance of muscle mass deposition and growth rate despite a hot environment. As FA can prevent protein damage by stimulating heat shock protein (Hsp's 32 and 70) expression (Ghosh et al., 2017), it is likely that free FA reduced serum AOPP levels by increasing chaperone HSP action.

Our results partially support our hypothesis, that free FA supplementation would enhance feedlot performance, carcass characteristics, wholesale cut yields and meat quality in heat-stressed hair ewe lambs by

Table 5
Effects of ferulic acid on carcass characteristics and body fat deposition of heat-stressed hair ewe lambs.

Items	Treatments[a]		SEM	P-Values
	Control	FA		
Hot carcass weight (kg)	14.73	14.55	0.18	0.48
Cold carcass weight (kg)	14.29	14.16	0.19	0.65
Hot carcass yield (%)[b]	60.86	61.04	0.67	0.85
Cold carcass yield (%)[b]	59.02	59.48	0.57	0.58
Conformation (units)	6.41	6.36	0.23	0.89
MLT area (cm^2)[c]	11.86	11.04	0.56	0.32
Morphometric measures (cm)				
Carcass length	55.23	54.82	0.59	0.63
Thorax depth	14.95	15.57	0.25	0.11
Leg length	24.18	24.27	0.38	0.87
Leg perimeter	40.75	39.55	0.43	0.07
Body fat				
Fat thickness (mm)	2.32	2.95	0.28	0.14
KPH (%)[d]	2.15	2.71	0.19	0.03
Omental (%)[b]	2.31	2.65	0.19	0.23
Mesenteric (%)[b]	1.78	2.21	0.11	0.02

[a] Ewe lambs fed 0 or 250 mg of free ferulic acid (FA) per kg of diet.
[b] Calculated expressing weights as a percentage of empty body weight.
[c] MLT area = *Longissimus thoracic* muscle area.
[d] KPH = Kidney-pelvic-heath fat, expressed as a percentage of hot carcass weight.

Table 6
Effects of ferulic acid on wholesale cut yields of heat-stressed hair ewe lambs.

Items[b]	Treatments[a]		SEM	P-Values
	Control	FA		
Forequarter (%)	51.75	53.66	0.46	0.01
Hindquarter (%)	48.25	46.33	0.46	0.01
Neck (%)	4.53	3.95	0.16	0.03
Loin (%)	11.70	12.35	0.27	0.10
Ribs (%)	8.18	8.80	0.23	0.08
Shoulder (%)	27.35	28.57	0.32	0.02
Plain loin (%)	11.25	10.48	0.24	0.04
Breast and flank (%)	5.45	6.21	0.23	0.04
Leg (%)	31.54	29.64	0.51	0.02

[a] Ewe lambs fed 0 or 250 mg of free ferulic acid (FA) per kg of diet.
[b] Weights expressed as a percentage of the half carcass.

Table 7
Effects of ferulic acid on weights of non-carcass components of heat-stressed hair ewe lambs.

Items[b]	Treatments[a]		SEM	P-Values
	Control	FA		
Blood (%)	5.46	5.68	0.18	0.39
Skin (%)	9.79	10.27	0.37	0.38
Head (%)	6.08	6.24	0.11	0.33
Feet (%)	2.89	2.91	0.04	0.72
Heart (%)	0.57	0.60	0.02	0.46
Kidney (%)	0.37	0.39	0.01	0.18
Liver (%)	2.26	2.26	0.04	0.90
Spleen (%)	0.22	0.23	0.01	0.95
Lungs (%)	1.52	1.43	0.04	0.14
Empty GT[c] (%)	7.33	7.29	0.19	0.90

[a] Ewe lambs fed 0 or 250 mg of free ferulic acid (FA) per kg of diet.
[b] Weights expressed as a percentage of the empty body weight.
[c] Empty GT = Empty gastrointestinal tract.

improving oxidative status, as the FA-fed ewe lambs had lower protein oxidation, better feedlot performance in the first days and higher yield of some wholesale cuts. However, free FA failed to improve overall oxidative status, carcass traits and meat quality.

Table 8
Effects of ferulic acid (FA) on meat quality of the *Longissimus thoracis* (LT) muscle of heat-stressed hair ewe lambs.

Items	Treatments[a]		SEM	P-Values
	Control	FA		
pH *postmortem*				
45 min	6.36	6.33	0.02	0.36
Ultimate (24 h)	5.73	5.70	0.02	0.26
Meat quality after aging[b]				
pH	5.72	5.68	0.03	0.11
Lightness (L*)	44.27	43.75	0.77	0.64
Redness (a*)	19.60	19.73	0.15	0.58
Yellowness (b*)	5.75	5.73	0.23	0.96
Hue angle (H*)	16.31	16.20	0.61	0.90
Chroma (C*)	20.44	20.57	0.17	0.62
WBSF[c] (N)	34.90	35.67	0.97	0.59

[a] Ewe lambs fed 0 or 250 mg of free ferulic acid (FA) per kg of diet.
[b] LT muscle was dissected, vacuum packed and aged during 14 d between 0 and 4 °C.
[c] WBSF = Warner-Bratzler shear force.

4.3. Feedlot performance

Feeding FA was effective in improving feedlot performance of heat-stressed hair ewe lambs in the first 10 d of the experimental period when conditions were hottest (i.e., Te > 35 °C) and the lambs had the highest OSI. This confirms the hypothesis raised in previous studies (Macías-Cruz et al., 2014; Wang, Wang, et al., 2019) which is that dietary supplementation of free FA enhances feedlot performance, but only in fattening lambs with high oxidative stress because of its antioxidant action. A similar growth response occurred in heat-stressed lambs fed feruloyl oligosaccharides (Wang, Meng, et al., 2019) while, in lambs with high oxidative stress caused by cold stress, feeding of free FA had positive effects on productivity (Wang, Wang, et al., 2019).

Some studies in murine model have reported that FA avoids HS-induced epithelial barrier dysfunction by activating the Nrf2/ARE pathway and Hsp32 expression (He et al., 2018), and that it prevents oxidative damage in pancreatic β-cells and improves insulin synthesis (Ghosh et al., 2017). In contrast, excessive reactive oxygen species (ROS) production in heat-stressed ruminants can cause intestinal epithelial injuries, resulting in lower nutrient absorption and high penetration of pathogens and endotoxins (Sejian et al., 2017). Finally, as HS promotes hyperinsulinemia to increase cellular glucose availability, avoids mobilization of body reserves and reduces synthesis of non-esterified fatty acids; this latter compound promotes pancreatic β-cell apoptosis (Baumgard & Rhoads, 2013). Thus, another possible reason for positive impacts on productive performance in the hottest period of the feeding phase could be because FA supplementation improved intestinal health and function, and also the glucose-insulin system.

On the other hand, supplemental FA did not exert long-term beneficial effects (day 10 to 40) on productive performance, which could be associated with a change in its mechanisms of action when heat and oxidative stress began to decline; this considering that internal fat deposition increased with FA feeding in the current study. Thus, free FA could have modulated energy metabolism at environmental temperatures <35 °C to increase internal body fat reserves in case of glucose depletion (Macías-Cruz et al., 2020). These findings suggest that FA supplementation in heat-stressed hair ewe lambs causes a long-term change in body gain composition by favoring energy efficiency.

4.4. Carcass and non-carcass traits, wholesale cut yields and meat quality

Supplementation of free FA did not change carcass and non-carcass traits in our heat-stressed ewe lambs, which we attribute to non-constant growth stimulation through the feedlot phase due to variable extents of heat stress experienced by lambs in the different feeding periods. These findings agree with reports in hair ewe lambs (Macías-Cruz

et al., 2014) and pigs (Li et al., 2015), but fed FA under thermoneutral conditions. In heat-stressed wool lambs, HCW and carcass yield were unaffected by using tannins and lycopene; also with antioxidant properties (Jiang et al., 2015; Liu et al., 2016). Despite this, free FA increased internal fat deposition in our sheep, which supports a possible increase in blood insulin concentrations and lipogenic gene expression (Naowaboot, Piyabhan, Munkong, Parklak, & Pannangpetch, 2016) due to FA under HS. A greater accumulation of internal fat in heat-stressed sheep represents an adaptive metabolic mechanism to have available energy in case of glucose depletion (Macías-Cruz et al., 2020).

In general, FA supplementation increased forequarter yield at a similar magnitude that it decreased hindquarter yield and, in consequence, this former beneficial effect of FA was not reflected in overall carcass weight and yield. However, most wholesale cut yields were improved by supplementing the FA, although neck, plain loin and leg yields decreased. This contrasts with findings previously published by our group at the same study site using hair ewe lambs in the absence of a thermal insult, i.e., no wholesale cut yield was affected by free FA (Macías-Cruz et al., 2014). This difference between studies suggests that there was an associative effect between HS conditions and FA supplementation to improve wholesale cut yields, mainly those directly involved in the respiratory tract function. Note that muscles, in consequence wholesale cuts, surrounding the ribcage have a higher proportion of oxidative than fast-glycolytic fibers (Ithurralde et al., 2015). Oxidative fibers compared with those fast-glycolytic have moderate to high fatigue resistance, insulin sensitivity, glucose oxidation, mitochondrial activity and ROS production (Yates et al., 2018). Indeed, both HS in sheep (Sejian et al., 2017) and FA in rats (Ghosh et al., 2017) have raised blood insulin levels and cell glucose uptake; additionally, the FA scavenges free radicals, promotes formation of slow oxidative fibers, and inhibits the activity of fast glycolytic fibers through Sirt1/MAPK pathway regulation (Chen et al., 2019). So, we hypothesized that improved metabolism in oxidative fibers due to combined effects of FA and HS led to muscle hypertrophy, which was reflected in higher yield of wholesale cuts where those muscle fibers predominated. Furthermore, as fast glycolytic fibers predominate in muscles of neck, plain loin and leg, it is likely that free FA supplementation can reduce muscle mass formation, and therefore, yields of those wholesale cuts.

That meat quality was not affected by feeding our ewe lambs with free FA under HS conditions is consistent with results in steers (González-Ríos et al., 2016) and pigs (Li et al., 2015) that were supplemented with FA in a thermoneutral environment. It should be noted that, as the ultimate pH, color and shear force in our meats were within normal ranges (Corazzin, Del Bianco, Bovolenta, & Piasentier, 2019), this suggests that hair breed sheep under chronic HS adapt to hyperthermia conditions and decrease oxidative damage in skeletal muscle. Thus, it is likely that the meat did not present a high oxidation and, consequently, free FA did not exert its antioxidant effects (Kubik, Tietze, Schmidt, Yates, & Petersen, 2018).

5. Conclusions

Free FA supplementation of heat-stressed hair ewe lambs improved growth and feed efficiency only when Te exceeded 35 °C due to its antioxidant activity; then, when Te and oxidative stress began to decline, it exerted lipogenic action and changed the body gain composition. In addition, FA improved internal fat deposition and yields of most wholesale cuts. However, it failed to enhance carcass characteristics and meat quality. Beneficial results could be associated with lower protein oxidation and better function of the glucose-insulin system. Effects of FA feeding on energy metabolism of heat-stressed hair lambs should be demonstrated in future research.

CRediT authorship contribution statement

Karen Mariela Valadez-García: Investigation, Formal analysis, Visualization, Writing - original draft. **Leonel Avendaño-Reyes**: Methodology, Funding acquisition, Writing - review & editing. **Raúl Díaz-Molina**: Validation, Writing - review & editing, Methodology. **Miguel Mellado**: Formal analysis, Writing - review & editing. **César A. Meza-Herrera**: Visualization, Writing - review & editing. **Abelardo Correa-Calderón**: Methodology, Writing - review & editing. **Ullses Macías-Cruz**: Methodology, Formal analysis, Funding acquisition, Conceptualization, Writing - original draft, Writing - review & editing.

Declaration of Competing Interest

The authors declare that they have no conflict of interest.

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