UNIVERSIDAD AUTÓNOMA DE BAJA CALIFORNIA

FACULTAD DE MEDICINA Y PSICOLOGÍA

“CONSUMO DIETÉTICO DE CAPSAICINA Y SU ASOCIACIÓN CON ADIPOSIDAD E HÍGADO GRASO EN UNA POBLACIÓN ADULTA MEXICANA”

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LISTA DE ABREVIATURAS

Abreviatura	Significado
ALP	Fosfatasa Alcalina
ALT	Alanina Aminotransferasa
AST	Aspartato Aminotransferasa
BAI	Body adiposity index (por sus siglas en inglés)
CASI	Centro de Atención Integral en Salud
CAP	Capsaicina
CC	Circunferencia de Cintura
DB	Bilirrubina Directa
FFQ	Cuestionario de Frecuencia Alimentaria
FLI	Fatty liver index
GLP1	Péptido Similar al Glucagón 1
GGT	Gamma Glutamil Transpeptidasa
HC	Circunferencia de cadera (por sus siglas en inglés)
HSI	Hepatic steatosis index (por sus siglas en inglés)
IMC	Índice de Masa Corporal
LDH	Láctica Deshidrogenasa
NAFLD	Enfermedad de hígado graso no alcohólica
OMS	Organización Mundial de la Salud
OECD	Organización para la Cooperación y el Desarrollo Económicos
PPAR-alfa	Receptor α Activado por Proliferador de Peroxisomas
SNAQ	Cuestionario de Apetito Nutricional
SNP	Polimorfismos de un solo nucleótido
TB	Bilirrubina Total
TRPV1	Receptor Transitorio Potencial Vanilloide 1
UABC	Universidad Autónoma de Baja California
UCP1	Proteína de Desacoplamiento 1
WC	Circunferencia de cintura (por sus siglas en inglés)

RESUMEN

“CONSUMO DIETÉTICO DE CAPSAICINA Y SU ASOCIACIÓN CON ADIPOSIDAD E HÍGADO GRASO EN UNA POBLACIÓN ADULTA MEXICANA”

Elaborado por: Yesenia Guadalupe Martínez Acevis

Resumen: La capsaicina (CAP) es el principal componente químico responsable del picor (dolor ardiente) de la planta de chile (*capsicum spp*), cuyas funciones metabólicas incluyen el equilibrio energético y la oxidación de ácidos grasos. El objetivo de este estudio es analizar la asociación del consumo dietético de capsaicina con marcadores de adiposidad e hígado graso en una población adulta mexicana.

Métodos: Este estudio transversal/analítico reclutó a 221 sujetos de 18 a 65 años residentes en la ciudad de Tijuana, Baja California, México. La ingesta diaria de CAP se analizó mediante un cuestionario validado de consumo de chile/CAP. Las mediciones antropométricas y bioquímicas se realizaron siguiendo protocolos estandarizados. Se aplicaron correlaciones de Pearson ajustadas para analizar la asociación de CAP con marcadores de adiposidad e hígado graso.

Resultados: En este estudio, el consumo promedio diario de CAP fue de 152,44 mg. El consumo dietético de CAP se correlacionó positivamente con el IMC (r= 0,179, p= 0,003), la circunferencia de la cadera (r= 0,176, p= 0,004) y el índice de adiposidad corporal (r= 0,181, p= 0,001. Asimismo, la ingesta diaria de CAP se correlacionó positivamente con índice de esteatosis hepática (r= 0,158, p= 0,004), índice de hígado graso (r= 0,141, p= 0,003) y lactato deshidrogenasa (r= 0,194, p= 0,016) después de ajustes estadísticos.

Conclusiones: Los resultados de este estudio sugieren. asociaciones positivas entre el consumo dietético de CAP y los marcadores de adiposidad corporal e hígado graso en una población adulta mexicana.

Palabras clave: capsaicina dietética, adiposidad, hígado graso, población mexicana.

1. Introducción

La capsaicina (CAP) es el principal componente químico responsable de la pungencia de la planta de chile (*capsicum spp*) (Sharma et al., 2013), cuyas funciones metabólicas incluyen el balance energético y la oxidación de ácidos grasos. En México se utiliza como ingrediente en platillos típicos y como acompañamientos preparados en forma de salsa (Román et al., 2013). Fisiológicamente interviene en procesos como la transducción del dolor, la respuesta inmune, el metabolismo de la glucosa, la función cardiovascular, la termogénesis y la saciedad (Ferdowsi et al., 2023). La CAP tiene efectos beneficiosos para la salud, entre ellas funciones analgésicas para el bloqueo del dolor, propiedades antiinflamatorias, regulación del metabolismo de la glucosa, reducción del riesgo de enfermedades de la piel, cáncer y enfermedades cardiovasculares (Azlan et al., 2022). Además de su papel en la termorregulación, el chile/CAP y sus componentes activos influyen en la modulación de la saciedad y la reducción del peso corporal. Investigar estas relaciones puede ofrecer una mejor comprensión del impacto del chile/CAP en la obesidad en México, facilitando el desarrollo de recomendaciones nutricionales personalizadas basadas en su consumo.

2. Antecedentes

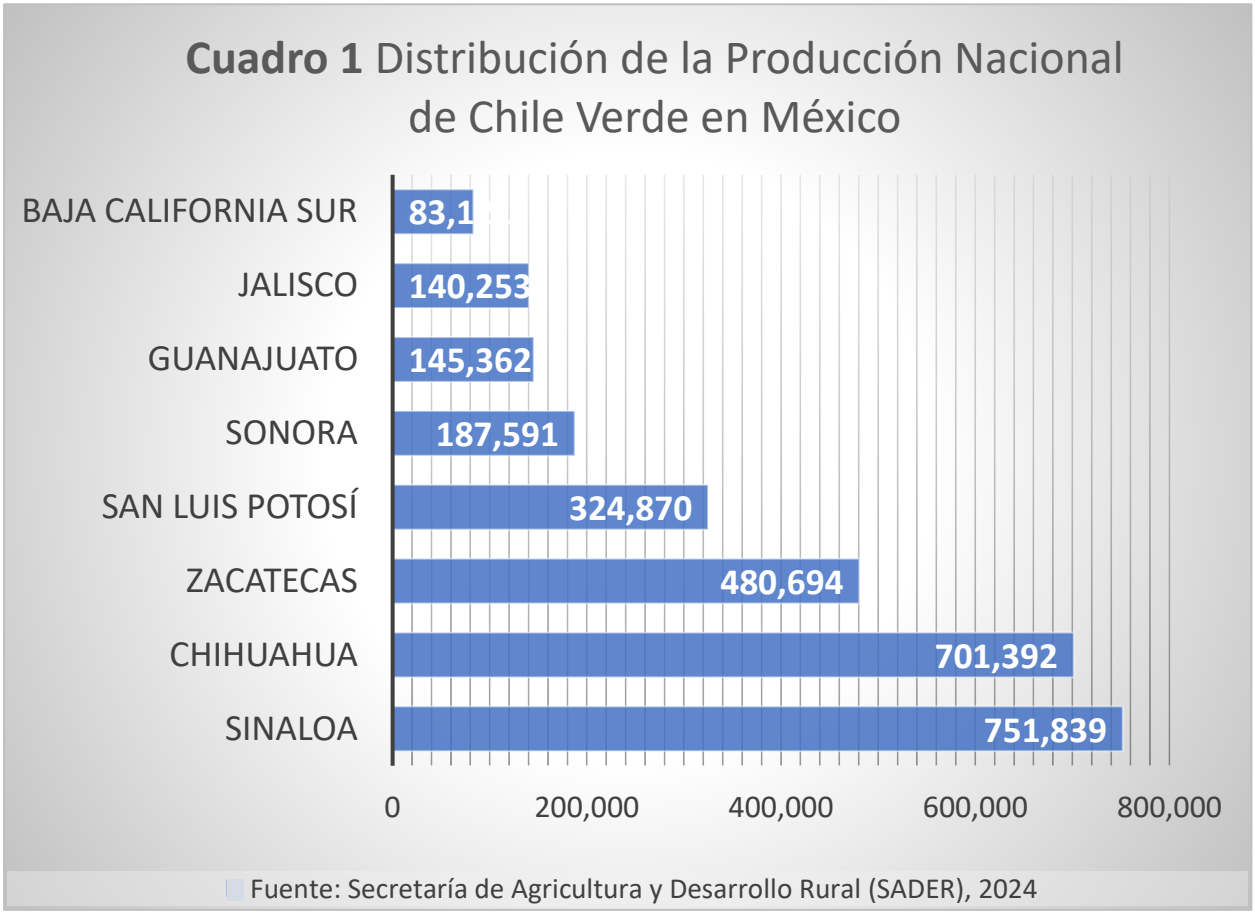
2.1. El chile y la alimentación

El chile es un ingrediente culinario distintivo de la cultura mexicana, que comúnmente se consume directamente en estado fresco, libre de procesamiento industrial y aditivos o como parte de platos preparados con chiles frescos y secos en preparaciones culinarias diarias o festivas (Aguilar-Meléndez et al., 2021).Estos tienen una larga historia de consumo para impartir sabor, color y conservar alimentos, así como una serie de usos en la industria farmacéutica y la medicina tradicional (Aguilar-Meléndez et al., 2021). Debido a su sabor amargo y picante, el chile ha jugado un papel importante en la gastronomía mexicana desde la época prehispánica y se utiliza típicamente como condimento o para acompañar una variedad de comidas (Román et al., 2013). Estos frutos se encuentran disponibles como recurso natural en una amplia gama de formas, tamaños, colores y sabores. Pertenecen al género Capsicum spp., que forma parte de la familia de las Solanáceas y cuenta con cinco especies domesticadas: *C. annuum , C. chinense , C. frutescens , C. baccatum y C. pubescens* (McCoy et al., 2023). Los chiles más consumidos en México son “jalapeño, serrano, habanero, de árbol, güero, manzano, chilaca, poblano y morrón”, mientras que los chiles secos son “piquín, catarino, pasilla, morita, chipotle, ancho, guajillo y mulato” (López-Carrillo et al., 2003). Estos chiles se consumen ampliamente en México, frescos o como ingredientes en una variedad de salsas para acompañar los platos. En la actualidad, varios grupos indígenas en México han salvaguardado los entornos tradicionales y locales relacionados con la producción de chile (Sharma et al., 2013). A pesar de que el uso del chile como ingrediente alimentario o culinario surgió en América hace aproximadamente 500 años, en la actualidad esta planta se ha extendido a países asiáticos, africanos, europeos y

americanos debido a procesos comerciales y culturales globales (Aguilar-Meléndez et al., 2021). Asimismo, la industria alimentaria ha utilizado derivados del chile para elaborar otros productos atribuibles al sabor, color y propiedades bactericidas de esta planta, los cuales se producen a gran escala y se distribuyen a nivel mundial (Aguilar-Meléndez et al., 2021). Además de su uso como especia común e importante para realzar el sabor, el chile también se aplica con fines medicinales para aliviar el dolor, como posible agente anestésico eficaz y en el tratamiento de diversas afecciones gastrointestinales (Aguilar-Meléndez et al., 2021).

2.2. Producción de chile en México

En el ámbito agrícola, México cultiva aproximadamente 50 tipos de chiles diferentes, los cuales constituyen el 20.6 por ciento del total de la producción de hortalizas en el país (AGRICULTURA Zacatecas, 2015). Entre estas variedades, se destaca el chile verde como uno de los principales productores situándose entre el segundo y cuarto lugar a nivel global. A finales de 2023, el país registró una producción de tres millones 237 mil toneladas y realizó exportaciones a 47 naciones, contribuyendo a que ocho de cada cien kilogramos de picantes en el mundo sean de origen mexicano (Secretaría de Agricultura y desarrollo rural, 2024). En cuanto a la distribución de esta producción, la Secretaría de Agricultura y Desarrollo Rural informa que Sinaloa, Chihuahua, Jalisco, Sonora y Zacatecas, en conjunto, aportan cerca del 67 por ciento del volumen nacional (Cuadro 1) (Secretaría de Agricultura y desarrollo rural, 2024).



2.3.Generalidades de la Capsaicina

La CAP es un compuesto extremadamente volátil, inodoro e hidrófobo responsable del sabor picante de la planta de chile (Sharma et al., 2013). La respuesta sensorial provocada por la CAP se conoce como pungencia, una irritación química que resulta de estímulos del nervio trigémino, siendo responsable de producir las sensaciones de calor y dolor en la boca (Sharma et al., 2013). La cantidad de CAP varía según el tipo de cultivo, maduración, ubicación, clima y fruto del chile, cuyo mayor volumen se localiza en la placenta, a excepción de los pimientos rojos, amarillos y verdes, que no contienen CAP (Batiha et al., 2020).

2.3.1 Implicaciones metabólicas de la Capsaicina

La CAP es absorbida por el tracto digestivo, particularmente por el yeyuno, el íleon y el duodeno, transportando así la capsaicina a la vena porta (Ortega Martínez et al., 1995). CAP participa en muchos procesos fisiológicos, incluida la transducción del dolor, la respuesta inmune, el metabolismo de la glucosa, la función cardiovascular, la termogénesis y la saciedad (Ferdowsi et al., 2023; Fischer et al., 2020; Panchal et al., 2018; Weng et al., 2021). Se han implicado varios objetivos en estas funciones, incluida la activación de varias vías de señalización, incluida la proteína quinasa activada por AMP/AKT, la transducción de calcio, el receptor transitorio potencial vanilloide 1 (TRPV1), el receptor α activado por proliferador de peroxisomas (PPAR-alfa), proteína de desacoplamiento 1 (UCP1) y péptido similar al glucagón 1 (GLP1) (Jia et al., 2024; Abdel-Salam & Mózsik, 2023; Ferdowsi et al., 2023; Takeda & Dai, 2022; Hui et al., 2020; Panchal et al., 2018). Además, la modulación de la abundancia y composición de la microbiota intestinal, así como la excitación de las neuronas sensoriales nociceptivas, se han identificado como posibles mecanismos subyacentes a los efectos fisiológicos de la CAP (Weng et al., 2021).

2.3.2 Capsaicina y tejido adiposo

Los adipocitos son células ricas en lípidos que se encuentran en el tejido adiposo, son un tipo especial de tejido conectivo. El tejido adiposo constituye entre el 20% y el 28% de la masa corporal en personas sanas; este porcentaje cambia según el sexo y el estado energético, por lo que la masa grasa puede representar hasta el 80% de la masa corporal

de una persona con exceso de adiposidad (Frigolet et al., 2020). Baskaran y colaboradores, observaron que el chile reduce directamente el gasto energético al activar el tejido adiposo marrón, dado que la CAP y el Capsiate mostraron un efecto protector contra la obesidad inducida por dietas altas en grasa en modelos de ratones y células in vitro, además de concluir que la pérdida de peso por el chile también fue el resultado de un mejor control de la insulina, por apoyar el control de peso y tener efectos positivos para el tratamiento de enfermedades como la obesidad, la diabetes y los trastornos cardiovasculares (Baskaran et al., 2018). Velmurugan Shanmugham y Ravi Subban realizaron una comparación del efecto de la CAP contra la obesidad en modelos de ratones inducidos por obesidad, como resultado después de administrar gránulos de CAP al 2%, la ganancia de masa en ratones por una dieta rica en grasas se redujo un 57.15 %, la concentración de niveles elevados de ácidos grasos libres fue de 0,0807±0,0060 µmol/mL, además de observar que las concentraciones de leptina disminuyeron un 46.15% en comparación con el grupo control (Shanmugham & Subban, 2022).

2.3.3. Controversias sobre la relación entre la capsaicina y la grasa corporal

En este contexto, estudios epidemiológicos han evaluado la asociación entre el consumo de chile/CAP y la adiposidad, con resultados controvertidos. Por ejemplo, un estudio prospectivo informó una asociación inversa entre la ingesta de chile y el riesgo de sobrepeso/obesidad en adultos chinos (Shi et al., 2017). De hecho, se observó que el consumo regular de compuestos capsaicinoides puede reducir la adiposidad abdominal, el apetito y la ingesta de energía, probablemente a través de la estimulación del receptor TRPV1 (Whiting et al., 2012). Mientras tanto, otro ensayo informó que la administración aguda de CAP fue capaz de aumentar el gasto energético en reposo sin cambios

subyacentes en la ingesta energética, el apetito y los niveles sanguíneos de péptidos orexigénicos/anorexigénicos en adolescentes y adultos jóvenes obesos (Rigamonti et al., 2018). En consecuencia, la administración aguda de CAP promovió el gasto energético y la oxidación de grasas en individuos aparentemente sanos (Janssens et al., 2013). La infusión intraduodenal de CAP aumentó significativamente la saciedad en voluntarios sanos sin afectar la liberación de hormonas de la saciedad (van Avesaat et al., 2016). Además, una revisión sistemática y un metaanálisis sugirieron que el consumo diario de capsaicinoides (*capsaicina, dihidrocapsaicina, nordihidrocapsaicina, homocapsaicina y homodihidrocapsaicina*) puede contribuir al control del peso corporal (Whiting et al., 2014). Un metaanálisis reciente indicó que la suplementación con CAP puede tener efectos modestos en la reducción del peso corporal, el índice de masa corporal (IMC) y la circunferencia de cintura (CC) en personas con sobrepeso u obesidad (W. Zhang et al., 2023). Por el contrario, se detectó un efecto opuesto en otra muestra china, donde el consumo de comida picante se asoció positivamente con medidas de adiposidad (especialmente obesidad central) en los hombres, pero no en las mujeres (Sun et al., 2014). Asimismo, se observaron mayores riesgos de sobrepeso y obesidad en los chinos que consumían chile con frecuencia (Xu et al., 2019). Otros estudios en asiáticos evidenciaron de manera similar asociaciones positivas entre el sabor picante y el consumo de chiles y alimentos picantes con niveles de obesidad general y abdominal (K. Yang et al., 2018, 2019; X. Yang et al., 2022). De hecho, un metaanálisis de los estudios transversales disponibles reveló un mayor riesgo de sobrepeso/obesidad en personas en la categoría más grande de ingesta de alimentos picantes en comparación con aquellos en la categoría más pequeña (M. Wang et al., 2023). Por lo tanto, se necesitan más estudios para dilucidar la asociación de la CAP con la adiposidad corporal y las

características metabólicas, teniendo en cuenta las características de las poblaciones de estudio, así como los factores culturales y ambientales relacionados de cada región.

2.4. Panorama general de la Obesidad e Hígado graso

En México existe una alta prevalencia de obesidad, donde más del 70% de la población total tiene sobrepeso u obesidad. De hecho, México es actualmente el segundo país más obeso del mundo (Dávila-Torres et al., 2015). Esta epidemia de obesidad es especialmente preocupante debido a su relación con el desarrollo de diversas enfermedades, entre las que se incluye la cirrosis hepática. En concreto, la cirrosis hepática es la cuarta causa de mortalidad entre los mexicanos, siendo el resultado del consumo excesivo de alcohol, la hepatitis viral y el hígado graso relacionado con la obesidad, las principales causas de enfermedad hepática en el país (Ramos-Lopez et al., 2015). La enfermedad por hígado graso se refiere a la acumulación excesiva de grasa en las células del hígado y es conocida como la principal causa de enfermedad hepática crónica a nivel mundial, afectando alrededor del 32.4% de la población (Elguezabal Rodelo et al., 2024) y un 44.4% en América latina (Younossi et al., 2023). A pesar de la carga de morbilidad, hasta la fecha no se han implementado estrategias efectivas en México para controlar la obesidad y la carga de enfermedad hepática. Además, no hay estudios disponibles que evalúen los efectos de la ingesta de CAP sobre la obesidad y el síndrome metabólico en individuos mexicanos. Explorar estas relaciones puede ayudar a dilucidar el papel del chile/CAP en el estado de obesidad en México para establecer recomendaciones nutricionales personalizadas basadas en la ingesta de chile/CAP. Por lo tanto, el objetivo de este estudio es analizar la asociación del consumo

dietético de CAP con marcadores de adiposidad e hígado graso en una población adulta mexicana.

3. Justificación

La Organización para la Cooperación y el Desarrollo Económicos (OECD, por sus siglas en inglés) (OECD, 2019) estima que el 60 % de los adultos tienen sobrepeso y, durante los próximos 30 años, este padecimiento será responsable de 92 millones de muertes en todo el mundo. Debido a los altos índices de obesidad en nuestra población y su impacto negativo en la salud pública y en la calidad de vida, es especialmente importante en México beneficiarse de este conocimiento puesto que el chile forma parte de nuestra identidad cultural y gastronómica desde épocas prehispánicas, como ha sido reconocido recientemente por el gobierno federal. Por tanto, este estudio es parte de una iniciativa para identificar la asociación entre la capsaicina de la dieta con la adiposidad e hígado graso. Esta información contribuirá a diseñar estrategias de nutrición personalizada basadas en el consumo de capsaicina para la prevención y el manejo preciso de obesidad e hígado graso.

4. Planteamiento del problema e hipótesis

4.1. Planteamiento del problema

México enfrenta una de las tasas más altas de sobrepeso y obesidad a nivel mundial, con una prevalencia superior al 70% en adultos y más del 40% de los habitantes de Baja California, según los criterios del IMC (ENSANUT, 2021). El problema de la obesidad y sus comorbilidades crónicas, como el hígado graso, la resistencia a la insulina y la diabetes mellitus, persiste como una preocupación de salud pública debido a sus efectos adversos y la escasez de estrategias efectivas para su prevención y tratamiento (Bischoff & Schweinlin, 2020; Kheniser et al., 2021). Actualmente, la prevalencia global de hígado graso afecta al 32.4% de la población, subrayando la urgencia de abordar esta creciente carga de enfermedades metabólicas (Elguezabal Rodelo et al., 2024). En esta investigación se explora la relación entre el consumo de capsaicina, la adiposidad y el hígado graso, proporcionando un mayor entendimiento del papel de este compuesto bioactivo en el metabolismo energético y la composición corporal.

4.2. Hipótesis

El mayor consumo de capsaicina se asocia con menores niveles de adiposidad e hígado graso en población mexicana.

5. Objetivos

5.1. Objetivo General

Analizar la asociación del consumo de capsaicina con la adiposidad e hígado graso en una población adulta mexicana.

5.2. Objetivos Específicos

1. Determinar el consumo de capsaicina por día en una población mexicana.
2. Analizar la asociación entre el consumo de capsaicina y los niveles de adiposidad en una población mexicana.
3. Analizar la asociación entre el consumo de capsaicina y la resistencia a la insulina, perfil de lípidos y pruebas de función hepática en una población mexicana.

6. Materiales y métodos

6.1. Diseño del estudio

Se realizó un estudio transversal analítico con una muestra de 221 sujetos adultos de 18 a 65 años residentes de la ciudad de Tijuana, Baja California en el Centro de Atención Integral en Salud (CAIS) de la Facultad de Medicina y Psicología de la Universidad Autónoma de Baja California (UABC).

6.2. Reclutamiento de participantes

6.2.1. Criterios de inclusión

Hombres o mujeres con edad mayor a 18 años, residentes de la ciudad de Tijuana, de nacionalidad mexicana, que no hayan seguido ninguna dieta los últimos 3 meses previos al estudio, sin historial clínico de trastornos tiroideos o metabólicos que requiera tratamiento (diabetes, hipertensión, dislipidemia grave y enfermedad coronaria). Individuos sin trastornos gástricos o problemas crónicos de los senos nasales, que acepten participar en el estudio conociendo los objetivos y firmen el formato de consentimiento informado (anexos).

6.2.2. Criterios de no inclusión

Mujeres embarazadas o lactantes; fumadores; bebedores de alcohol (más de 20 g/día y 40 g/día de ingesta de etanol en mujeres y hombres, respectivamente); individuos bajo cualquier medicamento recetado que pueda afectar la percepción del gusto y los niveles de lípidos en sangre; y sujetos con hipersensibilidad al chile/capsaicina.

6.2.3. Criterios de eliminación

Participantes que optaron por no participar en el estudio, no otorgaron su consentimiento informado o presentaron muestras de sangre insuficientes.

6.3 Consideraciones bioéticas

El protocolo del estudio fue presentado al Comité de Ética en Investigación de la UABC para su aprobación (código: D235, aceptado el 22 de octubre de 2019). Además, la investigación se llevó a cabo de acuerdo con los principios éticos para la investigación en humanos según la Declaración de Helsinki (World Medical Association, 2013). Los participantes fueron informados sobre los detalles y procedimientos del protocolo, quienes voluntariamente dieron su consentimiento informado por escrito (anexos).

6.4. Materiales y medición de variables

6.4.1. Estatura

La altura (cm) se midió con un estadiómetro clínico (Rochester Clinical Research, NY, USA). La estatura máxima se obtuvo utilizando la técnica de tracción de cuello. La cabeza se coloca en el plano de Frankfort, para evidenciar el vértex (la parte más prominente y alta de la cabeza). Se le indicó al sujeto que tome aire y sostenga una inspiración profunda manteniendo la cabeza fija, mientras el evaluador aplico una tracción de cuello moderada ubicando sus dedos medio e índice en el proceso mastoideo de ambos lados de la cabeza. El auxiliar del investigador coloco firmemente una escuadra metálica (estadímetro) sobre el vértex. La medida fue tomada al final de la tracción e inspiración profunda. Se tomó la lectura de la cantidad en centímetros al 0.1 cm más cercano. Se colocó a los participantes de pie, descalzos, con los pies juntos, rodillas extendidas, talones y espalda en contacto con la pieza vertical del aparato medidor. Los brazos permanecieron a los costados con las palmas dirigidas hacia los muslos. La pieza móvil horizontal del aparato se bajó hasta contactar con la cabeza del individuo, presionando ligeramente el cabello para tomar la lectura, según lo indicado.

6.4.2. Peso

El peso corporal (kg) se determinó mediante báscula Tanita SC-331S (analizador de composición corporal, Tanita Corporation, Japón), ajustada al 0.1kg con precisión de 100 g rango (0.1-130 kg). Antes de iniciar el registro de peso, se calibró la báscula mediante una pesa estándar. La medición se realizó sin zapatos, con ropa ligera, colocándose

encima de la báscula sin apoyarse en ningún otro sitio. Se escribió la cantidad registrada en la báscula.

6.4.3. Grasa corporal total (%)

Se determinaron mediante impedancia bioeléctrica utilizando la Tanita SC-331S (analizador de composición corporal, Tanita Corporation, Japón) siguiendo las instrucciones del fabricante.

6.4.4. Índice de masa corporal (IMC)

Se calculó dividiendo el peso corporal en kilos entre la altura en metros al cuadrado (kg/m2). La clasificación de bajo peso, normo peso, sobrepeso y obesidad se realizó de acuerdo con las recomendaciones de la Organización Mundial de la Salud (OMS) de la siguiente manera: <18.5, bajo peso; 18.5 a 24.9, normo peso; 25 a 29.9, sobrepeso; ≥ 30, obesidad.

6.4.5. Circunferencia de Cintura (CC)

En cm, se midió utilizando una cinta métrica ergonómica (SECA, Wandsbek, Germany) en sujetos de pie al final de una respiración natural, en el punto medio entre la parte superior de la cresta ilíaca y la costilla inferior en la línea medio axilar.

6.4.6. Presión Arterial

Se determinó utilizando el monitor de presión arterial digital de brazo automático Omron HEM-7120 (OMRON Corporation, Kioto, Japón) de acuerdo con los criterios estandarizados de la Organización Mundial de la Salud y la Sociedad Internacional de Hipertensión. Todos los parámetros se midieron por triplicado.

6.4.7. Relación cintura-cadera (WHR)

Se calculó dividiendo el WC por el HC

6.4.8. Índice de adiposidad corporal (BAI)

Se calculó mediante la fórmula BAI = [circunferencia de la cadera (cm) ÷ altura (m) 1,5] – 18

6.4.9. Índice de adiposidad visceral (VAI)

Se estimó mediante la fórmula VAI = (WC (cm)/ (39,68+(1,88×IMC)))× (triglicéridos/1,03) × (1,31/colesterol de lipoproteínas de alta densidad o HDL-c) para hombres y VAI = (WC (cm)/(36,58+(1,89*IMC)))×(triglicéridos/0,81)×(1,52/HDL-c) para mujeres.

6.5. Evaluación de la dieta

6.5.1. Variable de Evaluación de la ingesta dietética

La ingesta dietética habitual se evaluó utilizando recordatorios de 24 horas de tres días (anexos), los cuales han sido previamente utilizados en estudios nutrigenéticos similares (Ramos-Lopez et al., 2016, 2018). Se registraron datos como el tipo, la cantidad y el modo de preparación de todos los alimentos consumidos durante dos días de la semana y un día de fin de semana utilizando básculas de alimentos como modelos. Los recordatorios de 24 horas fueron procesados en el programa informático Nutrikcal (Nutrikcal VO®, México) con el fin de obtener las ingestas diarias promedio de macronutrientes y micronutrientes.

6.5.2. Consumo de Chile y Capsaicina

El método para estimar el consumo de chile y capsaicina se ha descrito previamente (López-Carrillo et al., 2003, 2012). Se utilizó un cuestionario de frecuencia alimentaria (FFQ)(anexos) semicuantitativo validado que comprende los tipos de chiles y platos preparados con chiles más consumidos en México (López-Carrillo et al., 2003, 2012). Se preguntó a los participantes con qué frecuencia consumieron chile durante los últimos tres meses de acuerdo con las siguientes categorías: Nunca; mensual; semanal; y diario. Este FFQ incluyó porciones de chile cuantitativas estandarizadas para estimar el tamaño de la porción consumida, ya sea en medidas domésticas o en gramos. La frecuencia del consumo de porciones predefinidas de chiles y platos preparados con chiles se multiplicó aún más por el contenido de CAP correspondiente de cada chile, dependiendo de sus

formas frescas o secas (López-Carrillo et al., 2003, 2012). La cantidad total de ingesta de CAP de cada sujeto se estimó sumando el contenido de CAP para el consumo diario informado de cada chile y plato de chile (López-Carrillo et al., 2003, 2012). Luego, los sujetos se estratificaron según las siguientes categorías de ingesta de CAP: consumidores ocasionales de CAP y consumidores diarios de CAP (1 a 100 mg/d; 100 a 400 mg/d; y 400 a 900 mg/d) para fines de comparación. Además, el apetito se evaluó mediante el cuestionario de apetito nutricional simplificado (SNAQ), una herramienta de cuatro ítems que comprende autoevaluaciones de apetito, saciedad, sabor de los alimentos y número de comidas por día (Lau et al., 2020). La puntuación total se utilizó como variable continua en análisis adicionales (rango de 4 a 20) (Lau et al., 2020).

6.6. Variables bioquímicas

Después de un ayuno nocturno de 12 horas, se extrajeron muestras de sangre en ayunas durante la noche y se centrifugaron adecuadamente para su posterior procesamiento del suero. Glucosa sérica, colesterol total, triglicéridos, HDL-c, proteínas totales, albúmina, globulinas, creatinina, láctica deshidrogenasa (LDH), aspartato aminotransferasa (AST), alanina aminotransferasa (ALT), gamma glutamil transpeptidasa (GGT), bilirrubina total (TB), bilirrubina directa (DB), fosfatasa alcalina (ALP), ácido úrico, calcio total, fósforo total, hierro total, creatina quinasa, sodio, potasio y cloro se determinaron utilizando kits comerciales apropiados y se leyeron en el Mindray BS-200. analizador (Mindray Medical International Limited, Shenzhen, China).

6.6.1. El colesterol unido a lipoproteínas de baja densidad (LDL-c) se calculó según la fórmula de Friedewald (Friedewald et al., 1972).

6.6.2. El índice de hígado graso (FLI) (Han, 2022) se ajustó de la siguiente manera FLI = (e(0,953 × ln(triglicéridos) + 0,139 × IMC + 0,718 × ln(GGT) + 0,053 × WC − 15,745))/(1 + e(0,953 × ln(triglicéridos) + 0,139 × IMC + 0,718 × ln (GGT) + 0,053 × WC − 15,745) × 100.

6.6.3. El índice de esteatosis hepática (HSI) (C. Wang et al., 2021) se ajustó como sustituto de la enfermedad hepática esteatósica de la siguiente manera: HSI = 8 × (ALT/AST) + IMC + 2 (si hay diabetes tipo 2) + 2 (si es mujer)

6.6.4. El índice de triglicéridos a glucosa (TyG) que refleja la resistencia a la insulina (Araújo et al., 2022) se estimó de la siguiente manera: ln (triglicéridos en ayunas [mg/dL] × glucosa en ayunas [mg/dL]/2).

6.6.5. Se calcularon los siguientes índices como marcadores de inflamación utilizando divisiones simples entre los siguientes parámetros como valores absolutos: proporción de neutrófilos a linfocitos (NLR); proporción de plaquetas a linfocitos (PLR); proporción de eosinófilos a basófilos (EBR); proporción de eosinófilos y linfocitos (ELR) y proporción de linfocitos y monocitos (LMR) (Gawiński et al., 2022; Man et al., 2021). Todos los

parámetros bioquímica serían debidamente controlados y calibrados con los reactivos de la marca Wiener Lab., en el Laboratorio de Bioquímica de la UABC.

6.7. Análisis de datos

Los valores de normalidad de las principales variables del estudio (ingesta de CAP, marcadores de adiposidad corporal y parámetros metabólicos) se verificaron mediante pruebas de Kolmogorov-Smirnov. Las variables continuas se expresaron como medias ± desviaciones estándar y las variables categóricas como número de casos. Las diferencias estadísticas en las variables antropométricas y bioquímicas entre las categorías de consumo de CAP se estimaron mediante pruebas ANOVA. Se aplicaron pruebas post hoc (Bonferroni) para determinar diferencias específicas entre los grupos de estudio. Se utilizaron correlaciones de Pearson para analizar la asociación entre el consumo de CAP y los marcadores de adiposidad corporal e hígado graso, que se ajustaron según variables de confusión, como sexo, edad, ingesta de energía y apetito. Los análisis estadísticos se realizaron utilizando los programas estadísticos IBM SPSS 20 (IBM Inc., Armonk, NY, EE. UU.). La significación estadística se estableció en un valor de $p < 0,05$.

7. Resultados

La tabla 1 muestra las características demográficas, antropométricas y clínicas de los consumidores y no consumidores de CAP, donde se puede observar que quienes consumen CAP diariamente tienen un mayor HC (p=0.032) y un BAI mayor (p=0.022) en comparación con quienes no consumen CAP. Por otro lado, no se observaron diferencias significativas en los niveles de presión arterial entre los dos grupos.

Tabla 1. Características demográficas, antropométricas y clínicas entre consumidores y no consumidores de chile (capsaicina)

	No consume (n= 37)	Consume (n=184)	P
Edad (años)	39.0±13.7	37.3±12.1	0.483
Sexo (F/M)	19/15	115/69	0.466
IMC (kg/m^2)	27.4±5.1	28.4±5.4	0.347
% grasa (%)	33.8±8.55	35.1±9.17	0.692
Cintura (cm)	89.2±16.2	90.2±14.2	0.728
Cadera (cm)	100±18.8	105±10.6	**0.032**
ICC	1.07±1.26	0.84±0.09	0.311
TAS (mmHg)	121±17.4	120±18.0	0.730
TAD (mmHg)	80.14±10.1	78.3±9.89	0.327
BAI	22.9±7.59	25.1±4.58	**0.022**
VAI	3.78±2.96	4.44±4.36	0.258

ICC: Índice cintura/cadera; BAI: Body adiposity index; VAI: Visceral adiposity index

Los análisis de características nutricionales no mostraron diferencias significativas en cuanto a apetito, calorías totales y porcentajes de proteínas, grasas y carbohidratos según el consumo de CAP. (Tabla 2)

Tabla 2. Características nutricionales entre consumidores y no consumidores de chile (capsaicina)

	No consume (n=37)	Consume (n=184)	P
Apetito	10.1±4.20	11.6±2.29	0.051
Kcal	1813±839	2328±1022	0.324
Proteínas (%)	21.5±15.5	18.2±4.51	0.702
Grasa (%)	41.7±12.8	41.6±9.65	0.984
Carbohidratos (%)	36.5±7.86	39.9±11.8	0.494

Las características metabólicas (parámetros bioquímicos de la función hepática, estado renal, perfiles de glucosa y lípidos) de la población categorizada por CAP evidenciaron niveles séricos más elevados de LDH (p = 0,030) y TB (p = 0,019) en los consumidores de CAP que sus homólogos, mientras que no se encontraron diferencias significativas para el resto de marcadores (Tabla 3).

Tabla 3. Características metabólicas entre consumidores y no consumidores de chile (capsaicina)

	No consume (n= 37)	Consume (n=184)	P
Glucosa en sangre (mg/dL)	95.6±21.4	94.3±11.9	0.843
Colesterol total (mg/dL)	191±39.5	191±38.3	0.987
Colesterol HDL (mg/dL)	43.6±11.1	46.0±13.5	0.249
Colesterol LDL (mg/dL)	128±36.2	123±34.2	0.443
Índice de colesterol HDL	4.58±1.20	4.37±1.29	0.358
Índice de colesterol HDL/LDL	3.14±1.23	2.88±1.12	0.199
Triglicéridos (mg/dL)	102±55.9	107±62.5	0.609

Índice de riesgo aterogénico (mg/dL)	20.5±11.1	21.7±13.0	0.576
Nitrógeno ureíco (mg/dL)	11.0±6.75	11.4±5.89	0.690
Urea (mg/dL)	23.5±14.4	24.5±12.6	0.690
Proteínas totales (g/dL)	7.38±0.49	7.46±0.46	0.298
Albúmina (g/dL)	4.04±0.19	4.02±0.18	0.444
Globulinas (calculada)	3.33±.048	3.44±0.47	0.178
Relación albúminas/globulinas (calculada)	1.43±0.31	1.40±0.33	0.619
Creatinina (mg/dL)	0.64±0.18	0.68±0.19	0.188
Relación BUN/creatinina (calculado)	20.6±16.7	18.9±11.9	0.562
Deshidrogenasa láctica (U/L)	179±91.6	226±125.4	**0.030**
Aspartato aminotransferasa (U/L)	44.0±41.0	36.8±11.7	0.292
Alanino aminotransferasa (U/L)	36.7±59.7	28.1±19.3	0.392
Gama glutamil transpeptidasa (U/L)	19.3±15.5	18.7±13.7	0.821
Bilirrubina total (µmol/L)	1.01±0.33	1.18±0.58	**0.019**
Bilirrubina directa (µmol/L)	0.14±0.06	0.16±0.08	0.064
Fosfatasa alcalina (U/L)	150±67.3	159±61.5	0.452
Ácido úrico (mg/dL)	5.41±1.89	5.47±1.90	0.873
Calcio total (mg/dL)	9.28±1.42	9.59±0.45	0.196
Fósforo total (mg/dL)	2.88±0.41	2.97±0.54	0.287
Hierro total (µmol/L)	90.6±33.6	86.0±34.1	0.451
Creatinin kinasa (U/L)	245±240.0	281±465.0	0.491
Sodio (mmol/L)	141±1.28	141±1.16	0.883
Potasio (mmol/L)	4.04±0.30	4.04±0.26	0.894
Cloro (mmol/L)	103±1.05	103±2.96	0.376
FLI	35.4±31.2	38.6±30.4	0.584
HSI	34.2±7.39	34.8±7.54	0.678
FIB-4	47.9±74.9	30.0±25.7	0.192
TyG	4.52±0.28	4.54±0.28	0.687
BARD	2.18±0.84	2.33±0.69	0.260
ZJU	230±65.0	234±68.9	0.783
FORNS	2.39±1.91	2.14±1.51	0.419

FLI: Fatty liver index; HSI: Hepatic steatosis index; FIB-4: Fibrosis-4; TyG: Triglycerides and glucose index; BARD: Score BARD, ZJU: Zhejiang University index; FORNS: Índice de FORNS.

Los perfiles inflamatorios de consumidores y no consumidores de CAP. Se puede observar que no existen diferencias entre ambos grupos (Tabla 4).

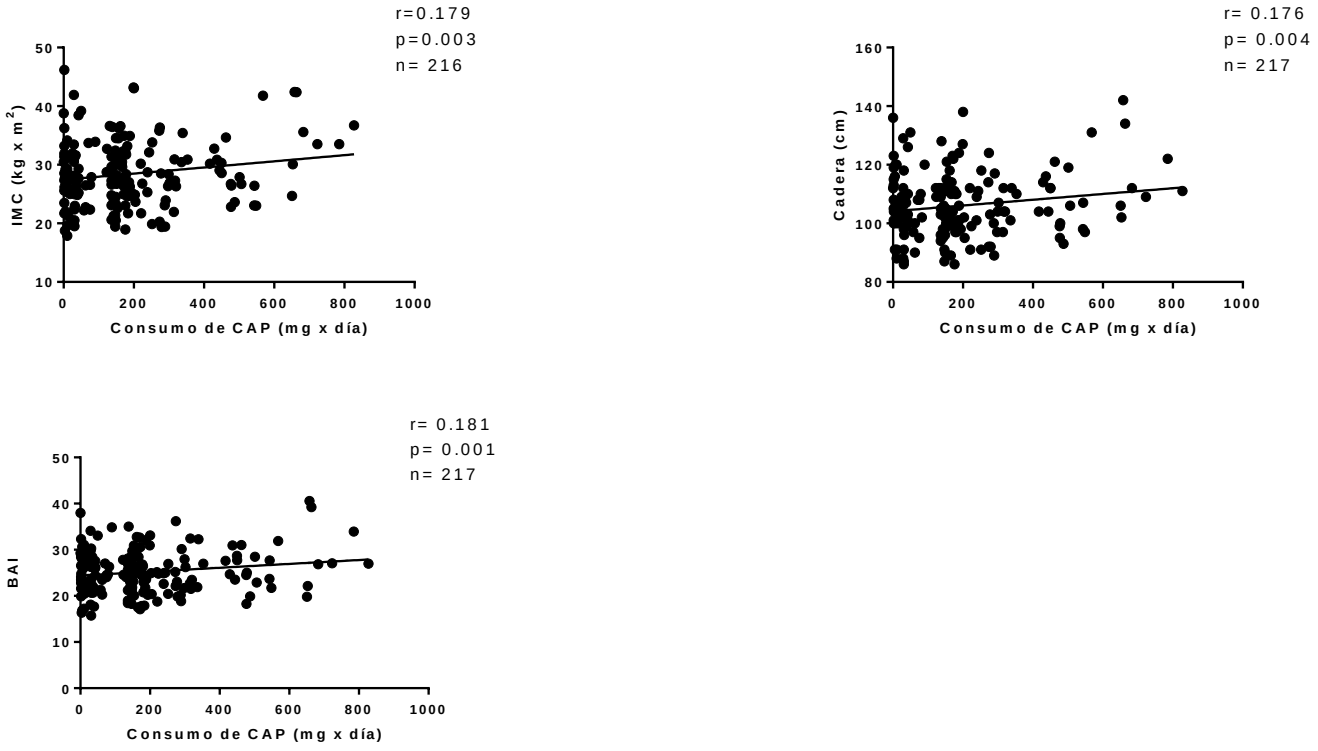
Tabla 4. Características inflamatorias entre consumidores y no consumidores de chile (capsaicina)

	No consume (n= 37)	Consume (n=184)	P
NLR	1.96±0.85	1.99±1.13	0.852
PLR	135±44.8	140±61.9	0.551
EBR	3.29±5.19	5.20±9.98	0.266
ELR	0.07±0.07	0.09±0.08	0.254
LMR	5.86±2.05	6.05±2.45	0.609

BLR: índice basófilos/Linfocitos, NLR: índice Neutrófilos/Linfocitos, PLR: índice Plaquetas/Linfocitos, EBR: índice Eosinófilos/Basófilos, ELR: índice Eosinófilos/Linfocitos, LMR: índice Linfocitos/Monocitos

La ingesta de CAP se correlaciona positivamente con el IMC (r = 0,179, p = 0,003), HC (r = 0,176, p = 0,004) y BAI (r = 0,181, p = 0,001) después de ajustes por edad, sexo, apetito, calorías, proteínas, niveles de ingesta de grasas y carbohidratos. (Fig. 1)

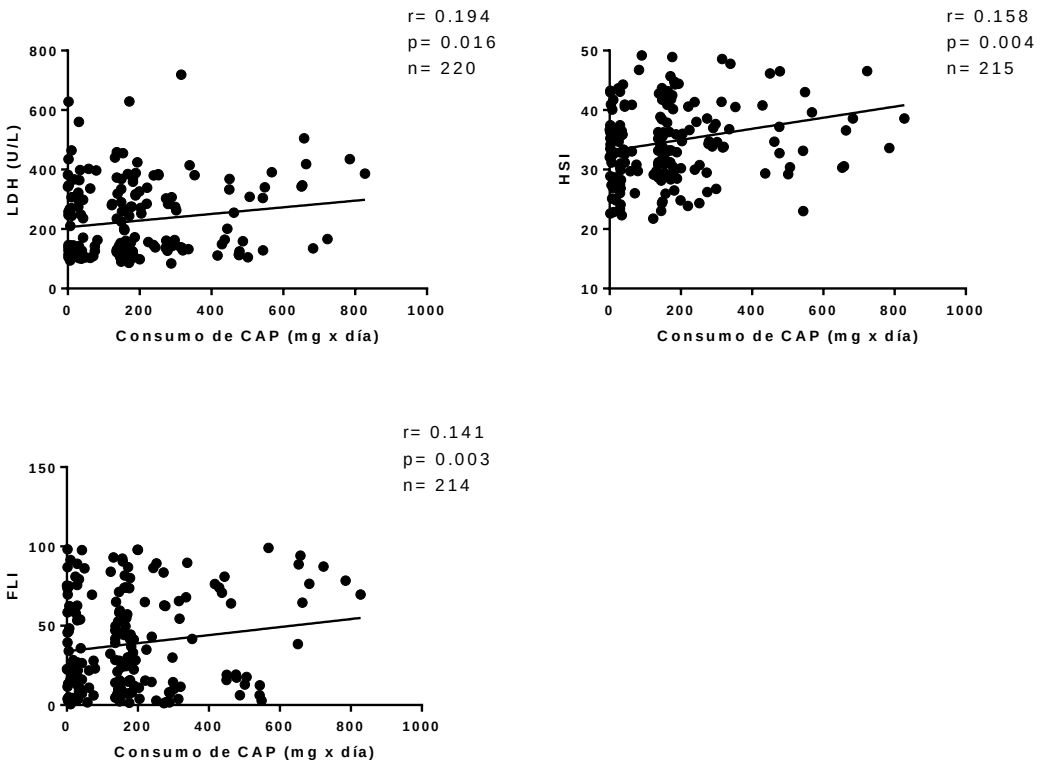
Fig. 1 Correlaciones entre el consumo de CAP y parámetros antropométricos



Los análisis están ajustados por edad, sexo, apetito, kilocalorías, ingestas de proteína, grasas e hidratos de carbono.

El consumo diario de CAP se correlaciona positivamente con HSI (r = 0,158, p = 0,004), FLI (r = 0,141, p = 0,003) y LDH (r = 0,194, p = 0,016) después de ajustes estadísticos (Fig. 2).

Fig. 2 Correlaciones entre el consumo de CAP y parámetros hepáticos



Los análisis están ajustados por edad, sexo, apetito, kilocalorías, ingestas de proteína, grasas e hidratos de carbono.

8. Discusión

La CAP es un compuesto reactivo picante con implicaciones sobre el estado de salud (Mosqueda-Solís et al., 2021). Los hallazgos de este estudio sugieren asociaciones positivas modestas pero significativas entre la ingesta de CAP y los marcadores de adiposidad (IMC, BAI y HC) e hígado graso (HSI, FLI y LDH) en la población mexicana adulta de Tijuana. Estos hallazgos pueden ayudar en el desarrollo de estrategias de intervención nutricional personalizadas para la obesidad y las enfermedades hepáticas basadas en los niveles de consumo de CAP. Sin embargo, dado que las tasas de correlación absoluta son moderadas, se necesitan estudios adicionales para validar nuestros resultados, tomando en consideración la dosis de CAP, así como para explorar las relaciones adicionales entre el consumo de CAP y la adiposidad/estado metabólico en otras regiones de México y en todo el mundo.

La fuente más importante de CAP comprende una variedad de chiles, pero su consumo varía entre regiones debido a diferencias alimentarias, culturales y sociales (Siebert et al., 2022). A la fecha existe escasa evidencia sobre la cantidad de CAP consumida por la población mexicana. En este estudio se encontró un alto nivel de consumo de CAP entre los participantes residentes en Tijuana (noroeste de México), con un promedio de 152.44 mg por día. Es de destacar que se reportaron niveles más bajos de CAP en diferentes áreas de México, incluidas Puebla (31.99 mg/d), Ciudad de México (29.84 mg/d) y Yucatán (24.54 mg/d), ubicadas en el centro y sur de México (López-Carrillo et al., 2003). Además, un estudio realizado en Corea estimó que el nivel máximo de consumo de CAP fue de 78,67 mg/d (Kwon, 2021). Por lo que se requieren más estudios

en todo el territorio mexicano y a nivel mundial con el fin de generar evidencia adicional sobre la ingesta de CAP y sus efectos en la salud.

Varios estudios respaldan el papel de la CAP en el metabolismo energético y la oxidación de grasas, aunque la magnitud de estos efectos es modesta (Ludy et al., 2012). En esta investigación se evidenció una asociación positiva: a mayor consumo de CAP, mayor nivel de adiposidad. Esto es consistente con los resultados de estudios epidemiológicos previos que muestran asociaciones positivas entre la ingesta de chile y las mediciones de obesidad basadas en el IMC, HC y BAI (Sun et al., 2014; M. Wang et al., 2023; Xu et al., 2019; K. Yang et al., 2018, 2019; X. Yang et al., 2022). Sin embargo, un punto importante de discusión es que los estudios previos que analizaron las asociaciones entre la ingesta de CAP y el estado de obesidad se centraron en los niveles de consumo de chile o condimentos picantes, pero no se estimó la cuantificación de CAP. Por lo tanto, es difícil comparar nuestros resultados con los informados en otros lugares, ya que el contenido de la CAP varía según el tipo de chile, la frecuencia de consumo y la forma de preparación culinaria (López-Carrillo et al., 2003, 2012). Además, se deben considerar las diferencias alimentarias, culturales, genéticas y sociales entre regiones (Siebert et al., 2022). Discernir las diferencias entre los análisis de los niveles de ingesta de chile y CAP es importante ya que los chiles contienen otros componentes nutricionales, como fibra, vitamina C y betacaroteno, que pueden influir en los niveles de equilibrio energético. Aunque los mecanismos precisos no se han aclarado completamente, se han postulado explicaciones plausibles para la relación positiva entre el consumo de chile y la predisposición a la obesidad, incluidos los procedimientos de cocción (se agrega aceite para hacer salsas de chile, lo que aumenta los niveles de aporte de energía) y el aumento de la ingesta de alimentos ricos en carbohidratos (pan y bebidas azucaradas) para aliviar

la sensación de ardor de los alimentos picantes (K. Yang et al., 2018). Si bien los análisis estadísticos se ajustaron adecuadamente, nuestros resultados muestran un aumento del apetito a medida que aumenta la ingesta de CAP, lo que no descarta por completo su influencia en los resultados de adiposidad. Además, se debe abordar la detección de otras variables, como el hambre y los antojos. Dada la evidencia inconsistente presentada hasta la fecha, se justifican investigaciones adicionales sobre los efectos de los niveles de ingesta de CAP sobre la adiposidad, incluidos estudios epidemiológicos longitudinales y ensayos aleatorios a largo plazo.

En modelos animales, la CAP dietética desencadenó el oscurecimiento del tejido adiposo blanco en ratones, contrarrestando la obesidad mediante la activación de mecanismos dependientes del canal TRPV1 (Baskaran et al., 2016). Es de destacar que la ingesta de CAP ejerció efectos contra la obesidad en ratones con dieta alta en grasas (HFD) a través de alteraciones en las poblaciones de microbiota intestinal (aumentos en el número de *Allobaculum , Coprococcus , Bacteroides , Prevotella , S24-7 , Akkermansia y Odoribacter* , como así como reducciones en *Sutterella , Helicobacter , Escherichia y Desulfovibrio*) y la producción de concentraciones intestinales de ácidos grasos de cadena corta, incluidos acetato y propionato (Y. Wang et al., 2020). En consecuencia, la administración de CAP en ratones HFD indujo una reducción significativa en los niveles de aumento de peso y la mejora de la tolerancia a la glucosa, lo que se relacionó con una mayor abundancia de Akkermansia muciniphila intestinal (Shen et al., 2017). Además, la aplicación tópica de CAP en ratones obesos limitó la acumulación de grasa en los tejidos adiposos al afectar los niveles de adipoquinas que involucran adiponectina, PPAR-alfa y gamma, visfatina, adipsina, factor de necrosis tumoral α e interleucina 6 (G. R. Lee et al., 2013).

En humanos, se informó una expresión reducida de TRPV1 en el tejido adiposo visceral de individuos obesos, que fue acompañada por una reducción del influjo de calcio inducido por CAP, destacando el potencial de activar los canales TRPV1 para prevenir la obesidad (L. L. Zhang et al., 2007). Además, el consumo dietético de CAP mostró efectos beneficiosos para el control del peso en humanos al reducir la ingesta de energía y desencadenar la actividad del tejido adiposo marrón, lo que lleva a un mayor gasto de energía a través de la termogénesis sin escalofríos (Zheng et al., 2017).

Además de la adiposidad, se ha informado de la implicación de la CAP en otros procesos metabólicos, como la función hepática, pero la investigación disponible se ha realizado principalmente en modelos animales (Karimi-Sales et al., 2024; Li et al., 2013; Shin et al., 2020). Por ejemplo, la ingesta crónica de capsaicina en la dieta previno la enfermedad del hígado graso no alcohólico (NAFLD, por sus siglas en inglés) en ratones a través de la activación del receptor δ (PPARδ) activado por el proliferador de peroxisoma mediado por TRPV1 (Li et al., 2013). En consecuencia, la aplicación tópica de capsaicina suprimió la acumulación de lípidos hepáticos mediante la regulación positiva de la β-oxidación y la lipogénesis de novo en ratones NAFLD inducida por dieta (Shin et al., 2020). En general, parece que el papel protector de CAP contra NAFLD está relacionado con la mejora de las alteraciones de los lípidos, el estrés oxidativo, la inflamación y la fibrogénesis, así como con mejoras en la disbiosis intestinal y aumentos en la producción de ácidos biliares (Karimi-Sales et al., 2024). Sin embargo, los estudios en humanos son escasos hasta la fecha. Los hallazgos del presente estudio muestran una asociación positiva entre la ingesta de CAP y los marcadores de hígado graso, siendo aparentemente el primer estudio en humanos que informa esta asociación. Este hallazgo puede estar relacionado con el aumento de la adiposidad observado en los consumidores

de CAP, que puede favorecer el depósito anormal de grasa en el hígado, pero no parece estar relacionado con la dieta ya que no se observan diferencias nutricionales entre los grupos de CAP. Aunque no se detectaron diferencias entre los grupos de CAP para las variables FLI, HSI y LDH en las pruebas ANOVA, estas se correlacionaron positivamente, lo que puede deberse al uso del consumo de CAP como variable lineal así como a la incorporación de covariables (edad , sexo, apetito, ingesta energética y de macronutrientes) en el entorno estadístico. Sin embargo, se requieren más estudios en humanos para confirmar nuestros resultados. Además, tanto HSI (J.-H. Lee et al., 2010) como FLI (Huang et al., 2015) fueron herramientas de detección válidas, simples y eficientes para el diagnóstico de esteatosis hepática incipiente, lo que respaldó su uso en nuestra investigación. Estudios observacionales comparables han implementado estos indicadores para evaluar las asociaciones entre factores dietéticos, la ingesta de nutrientes y alimentos específicos y NAFLD (Rietman et al., 2018), así como para explorar sus funciones como predictores de la sensibilidad individual a los cambios en el estilo de vida que comprenden la adherencia a un Régimen mediterráneo con restricción energética y actividad física (Martínez-Urbistondo et al., 2022).

Las fortalezas de este estudio incluyen la considerable muestra de sujetos analizados, con un poder estadístico (80%) similar a estudios previos comparables en la población mexicana que analizan las asociaciones entre la ingesta dietética y el riesgo metabólico (Ramos-Lopez et al., 2016, 2018). Para reducir el sesgo en nuestros resultados, las pruebas estadísticas se ajustaron a los factores de confusión, incluidos los niveles de ingesta de calorías totales, grasas, proteínas, carbohidratos y apetito, que podrían enmascarar las asociaciones entre el consumo de CAP y el estado de adiposidad/hígado graso. La aplicación del FFQ presentó algunas limitaciones, como errores sistemáticos y

sesgos en las estimaciones que presentan inexactitudes debido al listado incompleto de todos los posibles alimentos consumidos, errores en la frecuencia y tamaños habituales de las porciones y dependencia de la capacidad del encuestado para dar una respuesta a una pregunta sobre alimentación de acuerdo con las expectativas sociales, lo que resulta en sobreestimaciones o subestimaciones de ciertos niveles de consumo de alimentos (Pérez Rodrigo, 2015). Para abordar estos sesgos, utilizamos un cuestionario validado para determinar los niveles de consumo de CAP, que se basó en chiles mexicanos (frescos, secos o como condimentos en platos preparados) que normalmente se consumen en todo el territorio mexicano. Este instrumento fue supervisado por nutricionistas capacitados e incluyó tamaños de porciones predeterminados para mejorar la precisión de las estimaciones. Además, esta herramienta se ha utilizado anteriormente para explorar las asociaciones entre los niveles de consumo de chile y CAP con el riesgo de desarrollar cáncer gástrico en mexicanos (López-Carrillo et al., 2003, 2012), lo que refuerza su aplicación en nuestro estudio para estimar los niveles de ingesta de CAP. Por otro lado, algunas limitaciones incluyeron el hecho de que este fue un estudio transversal, por lo que no se pudieron inferir relaciones causales. Además, no se pudieron descartar por completo los errores estadísticos de tipo I y -2. Por lo tanto, se necesitan estudios epidemiológicos adicionales en otras regiones de México, así como ensayos experimentales que analicen los mecanismos a través de los cuales la CAP afecta la adiposidad y el estado hepático. Además, es importante analizar el papel de la genética asociada con la tolerancia a la CAP y cómo esto afecta el estado de salud. Por ejemplo, se ha informado que los polimorfismos de un solo nucleótido (SNP) en el gen TRPV1 influyen en algunos cambios sensoriales inducidos por CAP en sujetos aparentemente sanos, como una sensación de ardor (Okamoto et al., 2018) y

sensibilidad a la tos (Liviero et al., 2020). Asimismo, el amargor diferencial en CAP se asoció con SNP en el gen del miembro 38 del receptor 2 del gusto (TAS2R38) (Nolden et al., 2016). Además, las variaciones en los genes implicados en el metabolismo de CAP, como el miembro 1 de la subfamilia E de la familia 2 del citocromo P450 (CYP2E1), el miembro 9 de la subfamilia C de la familia 2 del citocromo P450 (CYP2C9) y el miembro 4 de la subfamilia A de la familia 3 del citocromo P450 (CYP3A4), pueden explicar las respuestas heterogéneas a la ingesta de CAP (Báez et al., 2010).

9. Conclusión

Aunque se debe tener precaución, los resultados de este estudio sugieren asociaciones modestas pero positivas entre el consumo dietético de CAP y los marcadores de adiposidad e hígado graso en una población adulta mexicana. Se necesitan más estudios para confirmar nuestros resultados, así como verificar el estado de otros indicadores metabólicos basados en la capacidad de ingesta de CAP.

Anexos

10.1.1. Consideraciones bioéticas

UNIVERSIDAD AUTÓNOMA DE BAJA CALIFORNIA

FACULTAD DE MEDICINA Y PSICOLOGÍA

Tijuana, Baja California, 22 de octubre del 2019
Oficio No. 1765/2019-2

DR. OSCAR OMAR RAMOS LÓPEZ
Presente.-

Por medio de este conducto, me permito informarle que se sometió a revisión a la Comisión de Bioética de esta Facultad, el proyecto de investigación: "GENETIC BASIS OF CHILLI CONSUMPTION (CAPSICUM SPP) AMONG THE MEXICAN POPULATION AND ITS EFFECTS ON BODY COMPOSITION AND METABOLIC TRAITS", el cual tuvo como resultado el siguiente dictamen: APROBADO (se anexa).

Sin más por el momento, me despido de usted enviándole un cordial saludo.

A T E N T A M E N T E
"POR LA REALIZACIÓN PLENA DEL HOMBRE"

DR. ARTURO JIMÉNEZ CRUZ
DIRECTOR

UNIVERSIDAD AUTÓNOMA DE BAJA CALIFORNIA
FACULTAD DE MEDICINA Y PSICOLOGÍA CAMPUS TIJUANA

C.c.p.- Dra. Ana Laura Martínez Martínez.- Coord. Posgrado e Investigación FMP
C.c.p.- Dirección
AJC/mca

UNIVERSIDAD AUTÓNOMA DE BAJA CALIFORNIA
FACULTAD DE MEDICINA Y PSICOLOGÍA
Comité de Bioética

Tijuana, Baja California a 22 de octubre del 2019

DR. ARTURO JIMÉNEZ CRUZ
DIRECTOR FACULTAD DE MEDICINA Y PSICOLOGÍA
PRESENTE.

Por medio del presente y aprovechando para extenderle un cordial saludo, se le notifica que, después de revisar la solicitud de aprobación del proyecto de investigación titulado:

"Genetic basis of chili consumption (Capsicum spp.) among the Mexican population and its effects on body composition and metabolic traits."

Investigador Principal: Dr. Oscar Omar Ramos López.

En comisión específica integrada por su servidor, el Comité de Bioética de la Facultad de Medicina y Psicología, ha decidido emitir el dictamen de:

APROBADO

Los fundamentos para dicha decisión se basan en que se trata de un proyecto clasificado como "tipo 2, investigación con riesgo mínimo" de acuerdo al Artículo 17 del Reglamento de la Ley General de Salud en Materia de Investigación para la Salud, al tratarse de una investigación que se basa en mediciones antropométricas y tomas de muestras sanguíneas por punción venosa. Se ha cuidado mantener el anonimato, la confidencialidad y la aplicación del consentimiento informado.

La presente aprobación es para su aplicación en un período no mayor a **DOS AÑOS** a partir de la fecha del dictamen; cualquier cambio al proyecto que implique cambio en los procedimientos, requiere de notificación a este Comité en un período no mayor a 15 días para mantener la vigencia del mismo.

Atentamente

"Por la Realización Plena del Hombre"

Dr. Rufino Menchaca Díaz.
Comité de Bioética FMyP

RECIBIDO
OCT 22 2019
FACULTAD DE MEDICINA Y PSICOLOGÍA

c.c.p. Archivo Comité de Bioética/D235

10.1.2. Consentimiento informado

Título del protocolo: *"Bases genéticas del consumo de chile (Capsicum spp.) y su asociación con la composición corporal y el perfil metabólico en una población mexicana: implicaciones para una nutrición personalizada".*

Sede del estudio: Facultad de Medicina y Psicología, Universidad Autónoma de Baja California, Tijuana, Baja California, México.

Invitación: A usted se le está invitando a participar en este estudio de investigación. Antes de decidir si participa o no, debe conocer y comprender cada uno de los siguientes apartados. Siéntase con la absoluta libertad para preguntar sobre cualquier aspecto que le ayude a aclarar sus dudas al respecto.

Propósito de la Investigación: Establecer las bases genéticas del consumo de chile entre la población mexicana y analizar sus efectos sobre la composición corporal y el estado metabólico. Con lo anterior se le podrán hacer recomendaciones personalizadas del consumo de chile con base en su perfil genético para la prevención y tratamiento de obesidad y alteraciones metabólicas asociadas.

Beneficios: Usted conocerá su peso y grasa corporal, la calidad de su dieta, sus niveles sanguíneos de glucosa y de perfil de lípidos e inflamatorio, y su perfil genético asociado al consumo de chile.

Procedimiento: En caso de aceptar participar en el estudio se le preguntarán algunos datos personales, así como preguntas relacionadas a sus hábitos de alimentación (especialmente acerca del consumo de chile) y sus antecedentes médicos. Además, se le tomarán medidas de estatura, peso, presión arterial, y se le la tomarán 2 muestras de sangre venosa para la determinación de pruebas bioquímicas y de ADN.

Riesgos e incomodidades: La extracción de sangre de la vena puede causar dolor, moretones, mareos y en raras ocasiones infección.

ACLARACIONES:

-Su decisión de participar en el estudio es completamente voluntaria.
-No habrá ninguna consecuencia desfavorable para usted, en caso de no aceptar la invitación.
-No tendrá que hacer gasto alguno por los estudios que se realicen dentro del servicio.
-No recibirá pago por su participación.
-En el transcurso del estudio usted podrá solicitar información actualizada sobre el mismo, al investigador responsable.
- Se utilizará su ADN para estudios genéticos.

Yo, _____he comprendido la información anterior y mis preguntas han sido respondidas de manera satisfactoria. Entiendo que los datos obtenidos en el estudio pueden ser duplicados o difundidos con fines científicos. Me han indicado también que todos los datos que proporcione a la persona autorizada que aplica la Historia Clínica, serán utilizados de **manera estrictamente confidencial** y serán considerados de manera anónima.

Acepto participar en este estudio de investigación.

_____
Fecha.

_____ _____

Nombre y Firma del Participante. **Persona quien aplico la Historia Clínica (Testigo 1)**

_____
Testigo (2)

Investigador principal: Dr. Oscar Omar Ramos López. Profesor-investigador de tiempo completo de la Facultad de Medicina y Psicología de la Universidad Autónoma de Baja California.

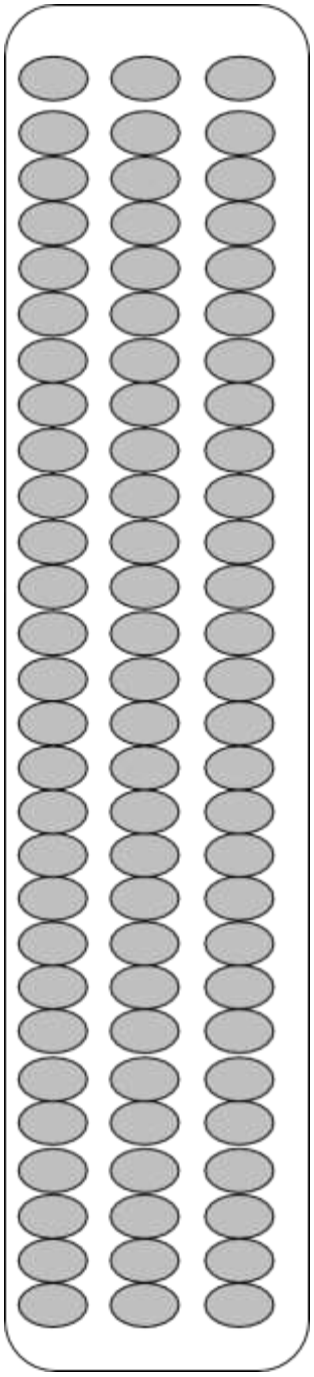
10.1.3. Recordatorio de 24 horas

DÍA ENTRE SEMANA	Alimento	Cantidad	Modo de preparación
Desayuno **Hora:**			
Comida **Hora:**			
Cena **Hora:**			
Colaciones **Hora:**			
DÍA ENTRE SEMANA	**Alimento**	**Cantidad**	**Modo de preparación**
Desayuno **Hora:**			
Comida **Hora:**			
Cena **Hora:**			

Colaciones **Hora:**			
DÍA FIN DE SEMANA	**Alimento**	**Cantidad**	**Modo de preparación**
Desayuno **Hora:**			
Comida **Hora:**			
Cena **Hora:**			
Colaciones **Hora:**			

10.1.4. Frecuencia de consumo de chiles

ALIMENTO **CHILES**	NUNCA	MENOS DE UNA	VECES AL MES	VECES A LA SEMANA			VECES AL DIA				Tipo de Cocción	BD
	(01)	(02)	1-3 (03)	1 (04)	2-4 (05)	5-6 (06)	1 (07)	2-3 (08)	4-5 (09)	6 + (10)	1 Crudo 2 Hervido o Cocido 3 Al Vapor 4 Horno o Asado 5 Microondas 6 Frito 8 No sabe	
69 Una cucharada Chile en salsa												
70 Chiles en lata											NA	
71 Chilaca												
72 Chile de agua												
73 Jalapeño o cuaresmeño												
74 Largo, güero o tornachile												
75 Serrano o verde												
76 Habanero												
77 Loco												
78 Manzano												
79 Poblano												
80 Ancho												
81 Cascabel												
82 Catarino												
83 Chipotle												
84 Guajillo												
85 Mulato												
86 Pasilla												
87 Criollo												
88 Piquín												
89 De árbol												
90 Morita												
91 Chiles en vinagre											NA	
92 Adobo												
93 Pipián												
94 Mole poblano												
95 Mole negro												
96 Otros												



Productos de la tesis

10.2.1. Póster en congreso nacional

El Comité Organizador del XIX Congreso Nacional de la Sociedad Española para el Estudio de la Obesidad (SEEDO)

CERTIFICA QUE

Yesenia Guadalupe Martínez Acevis, Ana Alondra Sobrevilla Navarro, Cindy Melissa Alcalá Zacarías, Oscar Omar Ramos López

han presentado la Comunicación Póster

con título

Consumo dietético de capaicina y su asociación con marcadores de adiposidad e hígado graso en población adulta mexicana

en el **XIX Congreso Nacional de la Sociedad Española para el Estudio de la Obesidad**,

celebrado en Sevilla, del 22 al 25 de noviembre de 2023.

Y para que así conste a todos los efectos, firman la presente.

En Sevilla a 25 de noviembre de 2023.

Dra. María del Mar Malagón
Presidenta de la SEEDO

Dr. Albert Lecube
Comité Organizador

Dr. Cristobal Morales
Comité Organizador

healthcare

MDPI

Article

Dietary Intake of Capsaicin and Its Association with Markers of Body Adiposity and Fatty Liver in a Mexican Adult Population of Tijuana

Yesenia Martínez-Aceviz [1], Ana Alondra Sobrevilla-Navarro [1,2] and Omar Ramos-Lopez [1,*]

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Abstract: Background: Capsaicin (CAP) is the main chemical component responsible for the pungency (burning pain) of the chili plant (*capsicum* spp.), whose metabolic functions include energy balance and fatty acid oxidation. The aim of this study is to analyze the association of dietary capsaicin consumption with markers of adiposity and fatty liver in a Mexican adult population. **Methods**: This cross-sectional/analytical study recruited 221 subjects aged 18 to 65 years who were resident in the city of Tijuana, Baja California, Mexico. The daily CAP intake was analyzed through a validated chili/CAP consumption questionnaire. Anthropometric and biochemical measurements were performed following standardized protocols. Adjusted Pearson's correlations were applied to analyze the association of CAP with adiposity and fatty liver markers. **Results:** In this study, the daily average consumption of CAP was 152.44 mg. The dietary CAP consumption positively correlated with BMI (r = 0.179, p = 0.003), hip circumference (r = 0.176, p = 0.004) and body adiposity index (r = 0.181, p = 0.001. Likewise, the daily CAP intake positively correlated with hepatic steatosis index (r = 0.158, p = 0.004), fatty liver index (r = 0.141, p = 0.003) and lactate dehydrogenase (r = 0.194, p = 0.016) after statistical settings. **Conclusions**: The results of this study suggest positive associations between dietary CAP consumption and the markers of body adiposity and fatty liver in a Mexican adult population.

Keywords: dietary capsaicin; adiposity; fatty liver; Mexican population

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1. Introduction

Chili is a distinctive culinary ingredient of Mexican culture, which is commonly consumed directly in fresh state (free of industrial processing or additives) or as part of dishes prepared with both fresh and dried chilies in daily or festive cooking preparations [1]. These have a long history of consumption to impart flavor, color and preserve foods, as well as a series of uses in the pharmaceutical industry and traditional medicine [1]. Due to its bitter and spicy flavor, chili has played an important role in Mexican gastronomy since pre-Hispanic times and is typically used as a condiment or to accompany a variety of meals [2]. These fruits are available as a natural resource in a wide range of shapes, sizes, colors and flavors, as they belong to the genus *Capsicum* spp., which is part of the Solanaceae family and has five domesticated species: *C. annuum*, *C. chinense*, *C. frutescens*, *C. baccatum* and *C. pubescens* [3]. The chilies most consumed in Mexico are "jalapeño, serrano, habanero, de arbol, güero, manzano, chilaca, poblano and bell pepper", while the dried chilies are "piquín, catarino, pasilla, morita, chipotle, ancho, guajillo and mulatto" [4]. These chilies are widely consumed in Mexico fresh or as ingredients in a variety of sauces/dips to accompany the dishes. At present, several indigenous groups in Mexico have safeguarded

traditional/local environments related to the production of chili [5]. Despite the use of chili as a food or cooking ingredient emerging in the Americas approximately 500 years ago, at present, this plant has spread to Asian, African, European and American countries due to commercial and global cultural processes [1]. Also, the food industry has used chili derivatives to produce other products attributable to the flavor, color and bactericide properties of this plant, which are produced on a large scale and distributed worldwide [1]. In addition to its use as a common and important spice-enhancing taste, chili is also applied for medicinal purposes in pain-relief, as a potential effective anesthetic agent, and in the treatment of various gastrointestinal complains [1].

Capsaicin (CAP) is an extremely volatile, odorless and hydrophobic compound responsible for the spiciness of the chili plant [5]. The sensory response caused by CAP is known as pungency, a chemical irritation that results from stimuli of the trigeminal nerve, being responsible for producing the sensations of heat and pain in the mouth [5]. The amount of capsaicin varies depending on the type of crop, ripening, location, climate and fruit of the chili, whose largest volume is located in the placenta, except for red, yellow and green peppers, which do not contain CAP [6]. CAP is absorbed by the digestive tract, particularly the jejunum, ileum and duodenum, thus transporting capsaicin to the portal vein [7]. CAP participates in many physiological processes, including pain transduction, immune response, glucose metabolism, cardiovascular function, thermogenesis and satiety [8–11]. Several targets have been implicated in these functions, including the activation of several signaling pathways, including AMP-activated protein kinase/AKT, calcium transduction, transient receptor potential vanilloid 1 (TRPV1), peroxisome proliferator-activated receptor α (PPAR-alpha), uncoupling protein 1 (UCP1) and glucagon-like peptide 1 (GLP1) [8,9]. Moreover, the modulation of the abundance and composition of gut microbiota as well as nociceptive sensory neurons excitation have been identified as potential mechanisms underlying the physiological effects of CAP [10].

In this context, epidemiological studies have evaluated the association between chili/capsaicin consumption and adiposity, with controversial results. A prospective study reported an inverse association between chili intake and the risk of being overweight/obesity in Chinese adults [12]. In fact, it was observed that the regular consumption of capsaicinoid compounds may reduce abdominal adiposity, appetite and energy intake probably via the stimulation of the TRPV1 receptor [13]. Meanwhile, another trial reported that the acute administration of CAP was able to increase resting energy expenditure without subjacent changes in energy intake, appetite and blood levels of orexigenic/anorexigenic peptides in obese adolescents and young adults [14]. Accordingly, the acute administration of CAP promoted energy expenditure and fat oxidation in apparently healthy individuals [15]. The intraduodenal infusion of CAP significantly increased satiety in healthy volunteers without affecting the release of satiety hormones [16]. Moreover, a systematic review and meta-analysis suggested that the daily consumption of capsaicinoids may contribute to body weight management [17]. Moreover, a recent meta-analysis stated that CAP supplementation may have modest effects on reducing body weight, BMI, and WC in overweight/obese individuals [18]. On the contrary, an opposite effect was detected in another Chinese sample, where the consumption of spicy food was positively associated with adiposity measures (especially central obesity) in males, but not in females [19]. Moreover, increased risks of being overweight and obese were observed in Chinese people who frequently consumed chili [20]. Other studies on Asians similarly evidenced positive associations between a spicy taste and the consumption of chilies and spicy foods with general and abdominal obesity levels [21–23]. Indeed, a meta-analysis of the available cross-sectional studies revealed an increased risk of being overweight/obese in individuals in the largest category of spicy food intake compared to those in the smallest category [24]. Thus, further studies are needed to elucidate the association of CAP with body adiposity and metabolic features, taking into account the characteristics of the study populations as well as the cultural and related environmental factors of each region.

In Mexico, there is a high prevalence of obesity, where more than 70% of the total population are overweight or obese. Indeed, Mexico is currently the second most obese country in the world [25]. Moreover, liver cirrhosis is the fourth leading cause of morality among Mexicans, being the result of excessive alcohol consumption, viral hepatitis, and obesity-related fatty liver, the main causes of liver disease in the country [26]. Despite disease burden, no effective strategies have been implemented in Mexico to control obesity and liver disease burden to date. In addition, no available studies assess the effects of CAP intake on obesity and metabolic syndrome in Mexican individuals. Exploring these relationships can help to elucidate the role of chili/CAP in obesity status in Mexico to establish personalized nutritional recommendations based on chili/CAP intake. Therefore, the aim of this study is to analyze the association of dietary CAP consumption with markers of adiposity and fatty liver in a Mexican adult population.

2. Materials and Methods

2.1. Participants

This cross-sectional/analytical study included a general sample of about 223 Mexican adult subjects, aged 18–65 years old, and from both genders. Apparently, healthy (by self-report) participants were randomly recruited from the "Centro de Atención Integral de la Salud (CAIS)" at the Faculty of Medicine and Psychology of the Autonomous University of Baja California (UABC), in the city of Tijuana, Baja California, Mexico. The recruitment process consisted of disseminating an invitation to participate in the study using the social media available at the UABC. Major exclusion criteria included a clinical history of diabetes, cardiovascular diseases (hypertension, coronary heart disease and cerebrovascular disease), thyroid disorders, ulcerative colitis, dyspepsia or related gastric problems; pregnant or lactating women; smokers; individuals with chronic sinus problems; subjects taking any prescribed medication that might affect their taste perception and blood lipid/glucose levels; and those who reported consuming a special diet that restricted nutrients or calories in the last three months prior to the study. Alcohol drinkers (consuming more than 20 g/d and 40 g/d of ethanol in women and men, respectively) were also excluded. Two individuals had diagnoses of hypothyroidism and were excluded. Thus, a total of 221 subjects were finally included in the study.

The study protocol was presented to the Research Ethics Committee of the UABC for approval (code: D235, accepted on 22 October 2019). Additionally, the research was conducted in accordance with the ethical principles for human research according to the Declaration of Helsinki [27]. Moreover, the participants were informed about the details and procedures of the protocol, who voluntarily provided written informed consent.

2.2. Anthropometric Measurements and Blood Pressure

A stadiometer (Rochester Clinical Research, New York, NY, USA) was used to estimate the height (cm) of the volunteers. Body weight (kg) and total body fat (%) were measured using a Tanita SC-331S (body composition analyzer, Tanita Corporation, Tokyo, Japan). Body mass index (BMI) was calculated by dividing body weight by squared meters (kg/m^2). Waist circumference (WC) was determined between the lower rib and top of the iliac crest, whereas hip circumference (HC) was measured over the great trochanters. A stretch-resistant tape was used to collect both circumferences. Waist to hip ratio (WHR) was calculated by dividing the WC by the HC. All anthropometric measurements were collected by trained nutritionists in a conditioned/equipped clinic in CAIS. The body adiposity index (BAI) was calculated as BAI = [hip circumference (cm) ÷ height (m) 1.5] − 18 [28], whereas the visceral adiposity index (VAI) was estimated as VAI = (WC (cm)/(39.68 + (1.88 × BMI))) × (triglycerides/1.03) × (1.31/high-density lipoprotein cholesterol or HDL-c) for males and VAI = (WC (cm)/(36.58 + (1.89*BMI))) × (triglycerides/0.81) × (1.52/HDL-c) for females [29]. The BAI is a useful measure of body fat percentage, which can be calculated from the HC and height only, with an accessible application in a clinical setting [28]. Furthermore, the BAI has been validated in individuals of Mexican ancestry with widely

varying adiposity levels [28]. Likewise, the VAI has been identified as a reliable parameter reflecting abdominal fat distribution and a promising tool to identify metabolic syndrome and cardiometabolic risk [29]. This index also uses conventional issues for its calculation, being simple to apply in epidemiological research. Both the BAI and VAI indices were calculated as complements of other conventional measurements of adiposity, such as BMI and fat percentage.

Systolic blood pressure (SBP) and diastolic blood pressure (DBP) were determined by triplicate following the standardized criteria using an automated sphygmomanometer [30].

2.3. Dietary Intake and Appetite

Habitual dietary intake was assessed using 24 h recalls, which were validated in the Mexican population [31,32]. Each subject was asked about the type, amount, and mode of preparation of all foods consumed during two weekdays and one weekend day using food scales as models. Dietary records were revised and coded by a trained dietitian using the Nutrikcal computer program (Nutrikcal VO®, Mexico City, Mexico) in order to obtain the average daily intakes of energy/calories and macronutrients (carbohydrates, fats and proteins). Moreover, a validated semi-quantitative food frequency questionnaire (FFQ) was used for estimating the CAP consumption that included the most consumed types of chilies and the dishes prepared with chili in Mexico [4,33]. The participants were asked how often they consumed chili during the past three months according to the following categories: never; monthly; weekly and daily [4,33]. This FFQ included standardized quantitative chili servings to estimate the portion size consumed either in household measures or grams. The frequency of the consumption of pre-defined portions of chilies and dishes prepared with chilies was further multiplied by the corresponding CAP content of each chili depending on fresh or dried forms [4,33]. The total amount of CAP intake of each subject was estimated by adding up the CAP content for the daily reported consumption of each chili and chili dish [4,33]. Then, the subjects were stratified according to the following CAP intake categories: occasional CAP consumers and daily CAP consumers (1–100 mg/d; 100–400 mg/d; and 400–900 mg/d) for comparison purposes. Furthermore, appetite was assessed using the simplified nutritional appetite questionnaire (SNAQ), a four-item tool comprising self-assessments of appetite, satiety, taste of food and number of meals per day [34]. The total score was used as a continuous variable in additional analyses (range from 4 to 20) [34].

2.4. Blood Tests

Overnight fasting blood samples were drawn and properly centrifuged for further serum processing. Serum glucose, total cholesterol, triglycerides, HDL-c, total proteins, albumin, globulins, creatinine, lactic dehydrogenase (LDH), aspartate ami-notransferase (AST), alanine aminotransferase (ALT), gamma glutamyl transpeptidase (GGT), total bilirubin (TB), direct bilirubin (DB), alkaline phosphatase (ALP), uric acid, total calcium, total phosphorus, total iron, creatine kinase, sodium, potassium and chlorine were determined using appropriate commercial kits and read on the Mindray BS-200 analyzer (Mindray Medical International Limited, Shenzhen, China). Low-density lipoprotein cholesterol (LDL-c) was calculated according the Friedewald formula [35]. The fatty liver index (FLI) [36] and hepatic steatosis index (HSI) [37] were fitted as proxies of steatotic liver disease as follows: HIS = 8 × (ALT/AST) + BMI + 2 (if type 2 diabetes) + 2 (if female); FLI = (e(0.953 × ln(triglycerides) + 0.139 × BMI + 0.718 × ln(GGT) + 0.053 × WC − 15.745))/(1 + e(0.953 × ln(triglycerides) + 0.139 × BMI + 0.718 × ln(GGT) + 0.053 × WC − 15.745) × 100. Moreover, the triglyceride to glucose index (TyG) mirroring insulin resistance [38] was estimated as follows: ln (fasting triglycerides [mg/dL] × fasting glucose [mg/dL]/2). In addition, the following indices were calculated as markers of inflammation using simple divisions between the following parameters as absolute values: neutrophil to lymphocyte ratio (NLR); platelet to lymphocyte ratio (PLR); eosinophil to basophil ratio (EBR); eosinophil to lymphocyte ratio (ELR) and lymphocyte to monocyte ratio (LMR) [39,40].

2.5. Statistical Analyses

The normality values of the main study variables (CAP intake, body adiposity markers and metabolic parameters) were verified by Kolmogorov–Smirnov tests. Continuous variables were expressed as means ± standard deviations, and categorical variables as number of cases. Statistical differences in the anthropometric and biochemical variables between CAP consumption categories were estimated using ANOVA tests. Post hoc (Bonferroni) tests were applied to determine specific differences between the study groups. Pearson's correlations were used to analyze the association between CAP consumption and markers of body adiposity and fatty liver, which were adjusted for confounding variables, including sex, age, energy intake and appetite. Statistical analyses were performed using the statistical programs IBM SPSS 20 (IBM Inc., Armonk, NY, USA). Statistical significance was set to p-value <0.05.

3. Results

Table 1 shows the demographic, anthropometric and clinical characteristics of consumers and non-consumers of CAP, where it can be observed that those who consume CAP daily have a larger HC ($p = 0.032$) and a higher BAI ($p = 0.022$) compared to those who do not consume CAP (Table 1).

Table 1. Demographic, anthropometric and clinical characteristics of the total population stratified by CAP consumption.

Variable	Occasional CAP Consumers (n = 37)	Daily CAP Consumers, 0–100 mg (n = 66)	Daily CAP Consumers, 100–400 mg (n = 93)	Daily CAP Consumers, 400–900 mg (n = 25)	p-Value
Age (years)	39.0 ± 13.72	38.8 ± 12.18	36.8 ± 12.18	35.2 ± 12.26	0.499
Sex (F/M)	19/15	115/69	115/69	115/69	0.891
BMI (kg/m^2)	27.4 ± 5.18	27.9 ± 5.70	28.1 ± 5.13	30.5 ± 5.92	0.147
Body fat (%)	33.8 ± 8.55	33.9 ± 10.3	34.5 ± 8.25	39.3 ± 8.74	0.260
WC (cm)	89.2 ± 16.2	89.5 ± 13.6	89.3 ± 14.1	95.3 ± 15.5	0.299
HC (cm)	103 ± 9.87	105 ± 10.6	104 ± 9.87	110 ± 12.3	0.074
WHR	0.85 ± 0.10	0.84 ± 0.08	0.85 ± 0.09	0.86 ± 0.10	0.875
SBP (mmHg)	121 ± 17.4	118 ± 21.5	121 ± 16.0	120 ± 15.5	0.817
DBP (mmHg)	80.1 ± 10.1	78.1 ± 10.3	78.6 ± 9.95	78.0 ± 9.93	0.779
BAI	22.9 ± 7.59	24.9 ± 4.62	24.8 ± 4.20	26.9 ± 5.51	**0.033** *
VAI	3.99 ± 2.90	4.17 ± 2.87	4.73 ± 5.47	4.09 ± 2.77	0.741

Values are presented as means ± standard deviations. Sex is represented as number of cases. Bold numbers indicate $p < 0.05$. F: female; M: male; BMI: body mass index; WC: waist circumference; HC: hip circumference; WHR: waist to hip ratio; SBP: systolic blood pressure; DBP: diastolic blood pressure; BAI: body adiposity index; VAI: visceral adiposity index. * Post hoc tests: occasional CAP consumers vs. daily CAP consumers, 400–900 mg, $p = 0.020$.

The nutritional characteristic analyses showed no significant differences concerning appetite, total calories and percentages of protein, fat and carbohydrates according to CAP consumption (Table 2).

Table 2. Nutritional characteristics of the total population stratified by CAP consumption.

Variable	Occasional CAP Consumers (n = 37)	Daily CAP Consumers, 0–100 mg (n = 66)	Daily CAP Consumers, 100–400 mg (n = 93)	Daily CAP Consumers, 400–900 mg (n = 25)	p-Value
Appetite	10.1 ± 4.20	11.5 ± 2.22	11.5 ± 2.35	12.0 ± 2.29	**0.029** *
Total calories	1898 ± 831	2205 ± 772	1975 ± 693	1995 ± 755	0.196

Table 2. *Cont.*

Variable	Occasional CAP Consumers (*n* = 37)	Daily CAP Consumers, 0–100 mg (*n* = 66)	Daily CAP Consumers, 100–400 mg (*n* = 93)	Daily CAP Consumers, 400–900 mg (*n* = 25)	*p*-Value
Proteins (%)	19.6 ± 9.89	18.3 ± 4.16	18.6 ± 4.06	20.8 ± 5.17	0.250
Fat (%)	38.4 ± 8.51	38.8 ± 8.36	37.0 ± 8.10	36.9 ± 6.9	0.533
Carbohydrates (%)	41.7 ± 12.4	41.8 ± 9.12	43.4 ± 9.30	41.8 ± 8.01	0.720

Values are presented as means ± standard deviations. Bold numbers indicate $p < 0.05$. * Post hoc tests: occasional CAP consumers vs. daily CAP consumers, 100–400 mg, $p = 0.023$; occasional CAP consumers vs. daily CAP consumers, 400–900 mg, $p = 0.033$.

The metabolic characteristics (biochemical parameters of liver function, kidney status, glucose and lipid profiles) of the population categorized by CAP evidenced higher serum levels of LDH ($p = 0.030$) and TB ($p = 0.019$) in CAP consumers than their counterparts, whereas no significant differences were found for the rest of the markers (Table 3).

Table 3. Metabolic characteristics of the total population stratified by CAP consumption.

Variable	Occasional CAP Consumers (*n* = 37)	Daily CAP Consumers, 0–100 mg (*n* = 66)	Daily CAP Consumers, 100–400 mg (*n* = 93)	Daily CAP Consumers, 400–900 mg (*n* = 25)	*p*-Value
Blood glucose (mg/dL)	95.6 ± 21.4	94.9 ± 12.5	95.0 ± 11.6	94.4 ± 11.4	0.989
Total cholesterol (mg/dL)	191 ± 39	191 ± 36	190 ± 37	195 ± 46	0.947
HDL-c (mg/dL)	43.6 ± 11.1	47.2 ± 13.1	45.0 ± 14.0	46.6 ± 12.9	0.548
LDL-c (mg/dL)	128 ± 36	123 ± 29	123 ± 36	127 ± 38	0.832
Triglycerides (mg/dL)	102 ± 55	105 ± 60	108 ± 64	109 ± 61	0.954
Urea (mg/dL)	23.5 ± 14.4	24.7 ± 11.9	24.2 ± 13.1	24.7 ± 12.7	0.971
Total proteins (g/dL)	7.38 ± 0.49	7.37 ± 0.44	7.52 ± 0.46	7.49 ± 0.46	0.155
Albumin (g/dL)	4.04 ± 0.19	4.00 ± 0.17	4.03 ± 0.19	4.01 ± 0.20	0.725
Globulins	3.33 ± 0.048	3.37 ± 0.46	3.49 ± 0.47	3.45 ± 0.45	0.232
Creatinine (mg/dL)	0.64 ± 0.18	0.70 ± 0.18	0.68 ± 0.20	0.65 ± 0.20	0.188
LDH (U/L)	179 ± 91	217 ± 125	225 ± 125	256 ± 124	0.087
AST (U/L)	44.0 ± 41.0	37.3 ± 15.5	36.2 ± 8.83	37.3 ± 10.1	0.241
ALT (U/L)	36.7 ± 59.7	28.0 ± 21.1	27.3 ± 17.2	31.4 ± 22.3	0.416
GGT (U/L)	19.3 ± 15.5	19.0 ± 15.3	1817 ± 11.1	20.1 ± 18.3	0.921
TB (µmol/L)	1.01 ± 0.33	1.22 ± 0.56	1.15 ± 0.62	1.20 ± 0.44	0.320
DB (µmol/L)	0.14 ± 0.06	0.17 ± 0.09	0.16 ± 0.07	0.18 ± 0.05	0.289
ALP (U/L)	150 ± 67	154 ± 57	163 ± 63	154 ± 64	0.692
Uric acid (mg/dL)	5.41 ± 1.89	5.27 ± 1.85	5.61 ± 1.99	5.45 ± 1.74	0.745
Total calcium (mg/dL)	9.28 ± 1.42	9.51 ± 0.50	9.65 ± 0.40	9.58 ± 0.42	0.064
Total phosphorus (mg/dL)	2.88 ± 0.41	2.98 ± 0.53	3.02 ± 0.57	2.76 ± 0.38	0.117
Total iron (µmol/L)	90.6 ± 33.6	84.6 ± 31.3	84.8 ± 36.4	94.3 ± 32.7	0.518
Creatine kinase (U/L)	245 ± 240	377 ± 696	236 ± 263	202 ± 198	0.156
Sodium (mmol/L)	141 ± 1.28	141 ± 1.22	141 ± 1.17	141 ± 1.03	0.931
Potassium (mmol/L)	4.04 ± 0.30	4.04 ± 0.24	4.04 ± 0.28	3.99 ± 0.24	0.708
Chlorine (mmol/L)	103 ± 1.05	103 ± 1.17	103 ± 3.99	103 ± 1.11	0.725
FLI	35.4 ± 31.2	36.3 ± 30.3	37.5 ± 29.4	48.1 ± 33.7	0.344
HSI	34.2 ± 7.39	33.9 ± 8.26	34.7 ± 6.89	37.6 ± 7.55	0.214
TyG	4.52 ± 0.28	4.52 ± 0.29	4.54 ± 0.28	4.55 ± 0.26	0.941

Values are presented as means ± standard deviations. HDL-c: high-density lipoprotein cholesterol; LDL-c: low-density lipoprotein cholesterol; LDH: lactic dehydrogenase, AST: aspartate aminotransferase; ALT: alanine aminotransferase; GGT: gamma glutamyl transpeptidase; TB: total bilirubin; DB: direct bilirubin; ALP: alkaline phosphatase; FLI: fatty liver index; HSI: hepatic steatosis index; TyG: triglyceride and glucose index.

Table 4 shows the inflammatory profiles of consumers and non-consumers of CAP. It can be observed that there are no differences between both groups (Table 4).

The correlations between CAP consumption and anthropometric parameters are plotted in Figure 1. CAP intake positively correlates with BMI (r = 0.179, $p = 0.003$), HC (r = 0.176, $p = 0.004$) and BAI (r = 0.181, $p = 0.001$) after adjustments by age, sex, appetite, calories, protein, fat and carbohydrate ingestion levels.

Table 4. Inflammatory characteristics of the total population stratified by CAP consumption.

Variable	CAP Non-Consumers (n = 37)	CAP Consumption 0–100 (n = 66)	CAP Consumption 100–400 (n = 93)	CAP Consumption 400–900 (n = 25)	p-Value
NLR	1.96 ± 0.85	1.84 ± 0.95	1.97 ± 1.02	2.44 ± 1.72	0.140
PLR	135 ± 44.8	132 ± 63.8	147 ± 64.8	137 ± 42.4	0.459
EBR	3.29 ± 5.19	4.80 ± 8.79	4.75 ± 8.04	7.90 ± 17.1	0.305
ELR	0.07 ± 0.07	0.08 ± 0.05	0.10 ± 0.09	0.08 ± 0.06	0.335
LMR	5.86 ± 2.05	5.97 ± 2.24	6.04 ± 2.29	6.32 ± 3.45	0.898

Values are presented as means ± standard deviations. NLR: neutrophil to lymphocyte ratio; PLR: platelet to lymphocyte ratio; EBR: eosinophil to basophil ratio; ELR: eosinophil to lymphocyte ratio; LMR: lymphocyte to monocyte ratio.

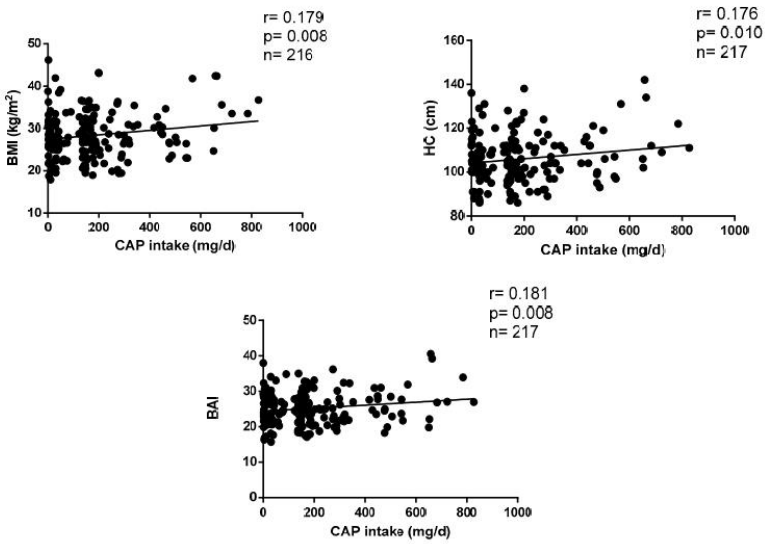

Figure 1. Correlations between CAP consumption and anthropometric parameters.

Figure 2 shows the correlations between CAP intake and metabolic markers of liver function. Daily CAP consumption positively correlates with HSI (r = 0.158, p = 0.004), FLI (r = 0.141, p = 0.003) and LDH (r = 0.194, p = 0.016) after statistical settings (Figure 2).

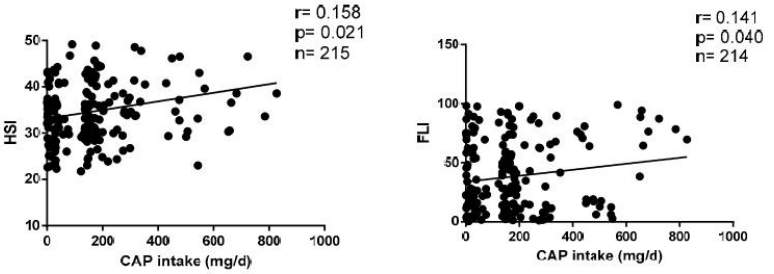

Figure 2. *Cont.*

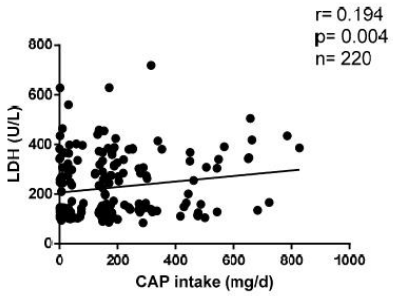

Figure 2. Correlations between CAP consumption and liver parameters.

4. Discussion

CAP is a spicy reactive compound with implications on health status [41]. The findings of this study suggest modest but significant positive associations between CAP intake and markers of adiposity (BMI, BAI and HC) and fatty liver (HSI, FLI and LDH) in the adult Mexican population of Tijuana. These findings may help in the development of personalized nutritional intervention strategies for obesity and liver diseases based on CAP consumption levels. However, since the absolute correlation rates are moderate, additional studies are needed to validate our results, taking into consideration CAP dosage, as well as to explore the additional relationships between CAP consumption and adiposity/metabolic status in other Mexican regions and worldwide.

The most important source of CAP comprises a variety of chilies, but its consumption varies between regions due to eating, cultural and social differences [42]. To date, there is scarce evidence concerning the amount of CAP consumed by the Mexican population. In this study, a high consumption level of CAP was found among participants living in Tijuana (Northwest Mexico), with an average of 152.44 mg per day. Of note, lower CAP levels were reported in different Mexican areas, including Puebla (31.99 mg/d), Mexico City (29.84 mg/d) and Yucatán (24.54 mg/d), located at the Center and South of Mexico. Moreover, a study conducted in Korea estimated that the maximum consumption level of CAP was 78.67 mg/d [43]. Therefore, further studies are required throughout the Mexican territory and worldwide in order to generate additional evidence concerning CAP intake and its effects on health.

Several studies support the role of CAP in energy metabolism and fat oxidation, although the magnitude of these effects is modest [44]. In this research, a positive association was evidenced: the greater the consumption of CAP, the higher the level of adiposity. This is consistent with the results of previous epidemiological studies showing positive associations between chili intake and obesity measurements based on BMI, HC and BAI [19–24]. However, an important point of discussion is that the previous studies analyzing the associations between CAP intake and obesity status focused on the consumption levels of chili or spicy condiments, but CAP quantification was not necessarily estimated. Therefore, it is difficult to compare our results with those reported elsewhere, since the CAP content varies depending on the type of chili, the frequency of consumption and the form of culinary preparation [4,33]. Moreover, eating, cultural, genetic and social differences between regions should be considered [42]. Discerning the differences between the analyses of chili and CAP intake levels is important since chilies contain other nutritional components, such as fiber, vitamin C and beta-carotene, which can influence energy balance levels. Although the precise mechanisms have not been completely elucidated, plausible explanations for the positive relationship between chili consumption and obesity predisposition have been postulated, including cooking procedures (i.e., oil is added to make chili sauces, increasing energy input levels), and the increased intake of carbohydrate-rich foods (i.e., bread and sugary drinks) to relieve the burning sensation of pungent foods [21]. While statistical analyses were appropriately adjusted, our results show an increase in appetite

as the CAP intake increases, which does not completely discard its influence on adiposity outcomes. Furthermore, the screening of other variables, such as hunger and cravings, should be addressed. Given the inconsistent evidence presented to date, additional investigations regarding the effects of CAP intake levels on adiposity are warranted, including longitudinal epidemiological studies and long-term randomized trials.

In animal models, dietary CAP triggered the browning of white adipose tissue in mice, counteracting obesity through the activation of TRPV1 channel-dependent mechanisms [45]. Of note, CAP intake exerted anti-obesity effects on high-fat diet (HFD) mice through alterations in gut microbiota populations (i.e., increases in the numbers of *Allobaculum*, *Coprococcus*, *Bacteroides*, *Prevotella*, *S24-7*, *Akkermansia* and *Odoribacter*, as well as reductions in *Sutterella*, *Helicobacter*, *Escherichia* and *Desulfovibrio*) and the production of intestinal short-chain fatty acid concentrations, including acetate and propionate [46]. Correspondingly, CAP administration in HFD-mice induced a significant reduction in weight gain levels and the improvement of glucose tolerance, which was related to a higher abundance of gut *Akkermansia muciniphila* [47]. In addition, the topical application of CAP to obese mice limited fat accumulation in adipose tissues by affecting adipokine levels involving adiponectin, PPAR-alpha and gamma, visfatin, adipsin, tumor necrosis factor-α and interleukin 6 [48].

In humans, a reduced TRPV1 expression in visceral adipose tissue from obese individuals was reported, which was accompanied by reduced CAP-induced calcium influx, highlighting the potential to activate TRPV1 channels to prevent obesity [49]. In addition, dietary CAP consumption showed beneficial effects for weight management in humans by reducing energy intake and triggering brown adipose tissue activity, leading to increased energy expenditure via non-shivering thermogenesis [50].

In addition to adiposity, the implication of CAP in other metabolic processes, such as liver function, has been reported, but the available research has mainly been conducted on animal models [51–53]. For example, chronic dietary capsaicin intake prevented non-alcoholic fatty liver disease (NAFLD) in mice through TRPV1-mediated peroxisome proliferator-activated receptor δ (PPARδ) activation [51]. Correspondingly, the topical application of capsaicin suppressed hepatic lipid accumulation through the upregulation of β-oxidation and de novo lipogenesis in diet-induced NAFLD mice [52]. Overall, it seems that the protective role of CAP against NAFLD is related to the amelioration of lipid alterations, oxidative stress, inflammation and fibrogenesis, as well as improvements in gut dysbiosis and increases in bile acid production [53]. Nevertheless, the studies on humans are scarce, to date. The findings of the present study show a positive association between CAP intake and markers of fatty liver, being apparently the first study on humans to report this association. This finding may be related to the increased adiposity observed in CAP consumers, which can favor abnormal fat deposition in the liver, but it seems not to be related to diet since no nutritional differences between CAP groups are observed. Although no differences between CAP groups were detected for the FLI, HIS and LDH variables in the ANOVA tests, these were positively correlated, which may have been due to the use of CAP consumption as a linear variable as well as the incorporation of covariates (age, sex, appetite, energy and macronutrient intakes) in the statistical settings. However, more studies on humans are required to confirm our results. Additionally, both HSI [54] and FLI [55] were valid, simple and efficient screening tools for the diagnosis of incipient liver steatosis, which supported their use in our investigation. Comparable observational studies have implemented these proxies to evaluate the associations between dietary factors (i.e., intake of specific nutrients and foods) and NAFLD [56], as well as to explore their roles as predictors of individual sensitivity to lifestyle changes comprising an adherence to an energy-restricted Mediterranean regime and physical activity [57].

The strengths of this study include the considerable sample of subjects analyzed, with a statistical power (80%) value similar to previous comparable studies on the Mexican population analyzing the associations between dietary intake and metabolic risk [31,32]. In order to reduce the bias in our results, statistical tests were adjusted for confounding

factors, including the intake levels of total calories, fat, protein, carbohydrates and appetite, which could mask the associations between CAP consumption and adiposity/fatty liver status. The application of FFQ presented some limitations, such as systematic errors and biases in the estimates presenting inaccuracies due to the incomplete listing of all possible foods consumed, errors in frequency and usual serving sizes and dependence on the respondent's ability to provide an answer question concerning eating according to social expectations, thus resulting in over- or under-estimations of certain food consumption levels [58]. To address these biases, we used a validated questionnaire to determine CAP consumption levels, which was based on Mexican chilies (fresh, dried or as condiments in prepared dishes) typically consumed throughout the Mexican territory. This instrument was supervised by trained nutritionists and included pre-determined portion sizes to improve the accuracy of the estimates. Moreover, this tool has been previously used to explore the associations between chili and CAP consumption levels with the risk of developing gastric cancer in Mexicans [4,33], reinforcing its application in our study to estimate CAP intake levels. On the other hand, some limitations comprise included the fact that this was a cross-sectional study, and therefore causal relationships could not be inferred. Moreover, type-I and -2 statistical errors could not be completely discarded. Thus, additional epidemiological studies in other regions of Mexico are needed, as well as experimental trials analyzing the mechanisms through which CAP affects adiposity and liver status. Furthermore, it is important to analyze the role of genetics associated with CAP tolerance and how this impacts health status. For instance, it has been reported that single nucleotide polymorphisms (SNPs) in the *TRPV1* gene influence some CAP-induced sensory changes in apparently healthy subjects, such as a burning sensation [59] and cough sensitivity [60]. Moreover, differential bitterness in CAP was associated with SNPs in the taste 2-receptor member 38 (*TAS2R38*) gene [61]. Additionally, variations in genes involved in the metabolism of CAP, such as cytochrome P450 family 2 subfamily E member 1 (*CYP2E1*), cytochrome P450 family 2 subfamily C member 9 (*CYP2C9*) and cytochrome P450 family 3 subfamily A member 4 (*CYP3A4*), may explain the heterogeneous responses to CAP intake [62].

5. Conclusions

Although caution should be exercised, the results of this study suggest modest but positive associations between dietary CAP consumption and markers of adiposity and fatty liver in a Mexican adult population. Further studies are needed to confirm our results as well as verify the status of other metabolic indicators based on CAP intake capacity.

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Institutional Review Board Statement: The study protocol was presented to the Research Ethics Committee of the UABC for approval (code: D235, accepted on 22 October 2019).

Informed Consent Statement: Informed consent was voluntarily provided by all subjects involved in the study.

Data Availability Statement: The data presented in this study are available on request from the corresponding authors.

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Conflicts of Interest: The authors declare no conflict of interest.

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Genetic Influence on Capsaicin Tolerance: Precision Nutrition Implications for Obesity Handling

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Capsaicin tolerance · Genetics · Polymorphism · Obesity · Precision nutrition

Abstract
Introduction: It has been suggested that capsaicin (CAP), a major pungent component in chili peppers, can be used as an anti-obesity ingredient due to effects on energy metabolism, but evidence is not consistent. Genetics may account for differences in CAP tolerance and its impact on adiposity status. The aim of this study was to systematically review current evidence concerning the role of genetic polymorphisms influencing CAP tolerance. *Methods:* The present systematic review analyzed and synthesized available evidence concerning associations between genetic polymorphisms and CAP tolerance following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols (PRISMA-P) guidelines. Databases such as PubMed/MEDLINE, Cochrane, Scopus, Google Scholar, SciELO, and LILACS were screened. Out of 228 publications identified, only 6 meet inclusion criteria and were finally included in the final report. *Results:* Overall, a total of 28 single nucleotide polymorphisms were associated with several CAP tolerance traits including sensitivity to burning/stinging, heat pain, and cough reactions, and detection of bitter taste thresholds. These genetic variants were located within 6 genes involved in key physiological processes such synthesis of tetrahydrobiopterin and nitric oxide production (*GCH1*), CAP uptake and transduction of thermal stimuli (*TRPV1*), and bitter taste perception (*TAS2R38*, *TAS2R3*, *TAS2R4*, and *TAS2R5*). *Conclusion:* There is evidence about the influence of genetic polymorphisms on CAP tolerance by affecting nociceptive signaling, CAP binding, and bitter tasting. This knowledge may facilitate the design and implementation of innovative CAP-based nutrigenetic strategies for a more precise clinical management of obesity.

Introduction

Obesity is one of the most important challenges in health systems, affecting more than 650 million adults and approximately 340 million children and adolescents worldwide [1]. Obesity is a complex and multifactorial metabolic disease, which is associated with an increased risk of many adverse medical conditions including type 2 diabetes, cardiovascular events, liver damage, and some

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types of malignancies [2]. In consequence, these obesity-related chronic diseases globally cause about 5.0 million deaths, with higher rates in males than in females [3]. In fact, obesity also increase morbidity and disability, representing a significant economic and social burden to most populations in terms of cost-of-illness and health-related quality of life [4].

Lifestyle modification (diet and exercise) continues to be the cornerstone for primary obesity treatment [5]. Moreover, natural bioactive food compounds have been explored for their anti-obesity properties [6]. In this regard, it has been postulated that capsaicin (CAP), a major capsaicinoid active component in chili peppers responsible for pungent flavor, can be used efficiently as an anti-obesity ingredient [7]. Accordingly, a systematic review of clinical trials evidenced that daily consumption of capsaicinoids may contribute to weight management via reductions in appetite and energy intake, although a high heterogeneity was found [8]. In addition, a meta-analysis of clinical trials suggested that CAP supplementation may have modest effects in weight loss in overweight or obese individuals, but more clinical investigation is recommended to confirm these findings [9].

Epidemiological studies have analyzed relationships between chili intake and obesity prevalence, with contradictory results. On the one hand, chili consumption was reported to be inversely associated with the risk of developing overweight/obesity in Chinese adults [10]. On the other hand, investigations in Asian populations support positive associations between the consumption of chili and spicy foods with general [11] and abdominal obesity levels [12–14]. Also, a recent study in Mexican individuals suggested positive associations between dietary CAP intake and markers of body adiposity and fatty liver [15]. These findings may be related to geographic and environmental differences between populations influencing food intake and behavior but also to intrinsic factors affecting CAP metabolism and energy homeostasis, including genetics. Indeed, investigating the genetic influence on CAP use may explain, at least in part, some of the inconsistencies among observational studies relating CAP to risk of obesity. Furthermore, because the mechanism of action is not presently fully understood, additional research is needed to clarify if the putative effects of CAP on adiposity are related to metabolic or eating behavior features.

The aim of this article was to systematically review current evidence concerning the role of genetic polymorphisms influencing CAP tolerance. This information may lead to the design of genotype-based nutritional strategies for obesity management based on precise CAP consumption.

Methods

Search Strategy and Eligibility Criteria

The present systematic review analyzed and synthesized available evidence concerning associations between genetic polymorphisms and CAP tolerance, with no restrictions in year of publication. Methodological procedures were performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols (PRISMA-P) guidelines [16]. Databases such as PubMed/MEDLINE, Cochrane, Scopus, Google Scholar, SciELO, and LILACS were screened. Reference lists of review articles were also scrutinized. Publications written only in English language were included. The search strategy included the following Medical Subject Headings (MeSH) terms: "capsaicin" OR "capsicum" OR "capsiate" OR "capsaicin tolerance" OR "capsaicin sensitivity" OR "capsaicin metabolism" OR "chili hotness" OR "chili pepper" OR "hot pepper" AND "genetic variant" OR "gene" OR "genomic" OR "polymorphism". Inclusion criteria comprised any type of study (observational, cross-sectional, cohort, case-control, clinical trials), available in full text, involving healthy subjects, children and adults, that evaluated the consumption of chili in the diet or the use of any method (oral or topical) of CAP use and that determined any genetic variant. Studies published as summaries or unpublished data, duplicate documents, animal or in vitro studies, languages other than English, review articles and meta-analysis were excluded. The screening was replicated at different times to guarantee reproducibility, and four researchers (ORL, YMA, AASN, and JRCM) performed independently the research. For the analysis and synthesis of the articles, a consensus of researchers (YMA, AASN, and ORL) was carried out to evaluate the quality and eligibility of each study according to the title and summary. Papers that meet the criteria from the selection phase were used in the data extraction phase.

Data Extraction

Overall, a total of 228 publications were identified: PubMed (n = 39), Scopus (n = 48), Cochrane (n = 13), Google scholar (n = 41), LILACS (n = 9), SciELO (n = 65), and reference lists of all relevant articles (n = 13). After deleting the duplicates (n = 9), the summaries of the remaining articles were examined (n = 200). Studies that did not meet the inclusion criteria (n = 187) were eliminated, resulting in 13 articles for full-text assessment for eligibility. Of these, 7 were further excluded. Finally, 6 articles were finally included in the present review (Fig. 1).

Results

According to selected studies, it was found that some genetic polymorphisms have an effect on CAP tolerance. The methodological details of the selected studies are summarized (Table 1). All included studies had a cross-

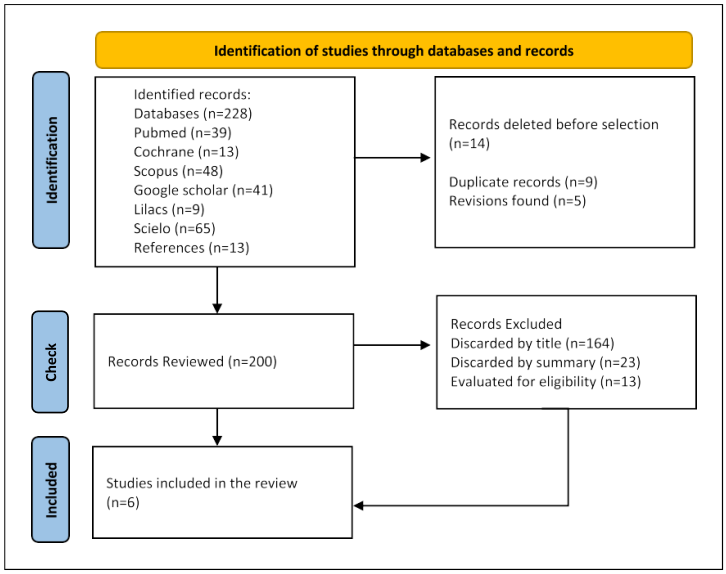

Fig. 1. PRISMA flow diagram summarizing the selection of papers included in this systematic review.

sectional design, and populations screened were heterogeneous, including Asians, Europeans, African, and Americans.

Overall, a total of 28 single nucleotide polymorphisms (SNPs) were associated with CAP tolerance. These genetic variants were located within 6 genes involved in key physiological processes such synthesis of tetrahydrobiopterin (BH4) and nitric oxide production (*GCH1*), CAP uptake and transduction of thermal stimuli (*TRPV1*), and bitter taste perception (*TAS2R38*, *TAS2R3*, *TAS2R4*, and *TAS2R5*). SNPs were distributed as follows: *GCH1* (n = 3), *TRPV1* (n = 18), *TAS2R38* (n = 3), *TAS2R3* (n = 1), *TAS2R4* (n = 1), and *TAS2R5* (n = 2).

The main tests that were performed to measure tolerance to CAP were sensitivity to burning/stinging, heat pain, and cough reactions, and detection of bitter taste thresholds (Table 1).

For instance, it was analyzed the association of SNPs within the *GCH1* gene and pain ratings induced by topical application of CAP in 39 healthy participants. Tests revealed that pain intensity was higher in rs4411417 T/T and C/T, rs3783641 T/T, and rs752688 C/C genotype carriers after CAP administration [17].

Moreover, it was investigated the effect of the *TRPV1*-variant rs8065080 (1911A>G, I585V) on thermal sensitivity in 25 healthy subjects [18]. Of note, GG genotype carriers experienced less CAP-induced warm hypoesthesia in warm-detection and less CAP-induced heat pain sensitivity, suggesting an altered channel function in this genetic profile [18]. This same variant was tested to influence CAP cough challenge sensitivity in men, where a diminished capsaicin sensitivity was due to the *TRPV1*-V585 mutation, as corroborated after in vitro assays [19].

Of note, four combined *TRPV1* SNPs, 315M (rs222747), 585I (rs8065080), 469I (rs224534), and 91S (rs222749) explained higher cough sensitivity to a CAP challenge in healthy subjects [20]. Besides, higher burning pain sensitivity to CAP was associated to the following *TRPV1* SNPs: 2193 CT (rs460716), 14727 CG, 17775 CG (rs161385), 30580 AG (rs57716901)/30599 TG (rs61387317) haplotype, and 43524 TT + TG (rs4790523) in Japanese adults [21]. In addition, higher oral CAP sensitivity was related to the following *TRPV1* variants: 19274 GA, 21003 TT/21682 TT/24752 AA haplotype, 30580 AA/30599 TT haplotype, 33554 GG, 33605 AA, 43524 TT, 37280 TT, and 39341 TT in this same population [21].

Furthermore, variability in perceived bitterness of CAP was significantly associated with *TAS2R38* and *TAS2R3/4/5* diplotypes [22]. Thus, PAV homozygotes for the *TAS2R38* gene perceived greater bitterness from CAP on circumvallate papillae, compared to heterozygotes and AVI homozygotes. Similarly, CCCAGT homozygotes of *TAS2R3/4/5* diplotypes rated the greatest bitterness of CAP, compared to heterozygotes and TTGGAG homozygotes [22].

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Table 1. Summary of relevant studies analyzing the genetic influence on CAP tolerance

Study design	Population	Gene	Gene function	Polymorphism	Methodology	Results	Reference
CS	Healthy young adults (European Americans, Africans, and Asians), *n* = 39	*GCH1*	Amino acid metabolism and neurotransmitter production	rs4411417 (C/T) rs3783541 (T/A) rs7526887 (C/T)	CAP-induced pain CAP-induced pain stimulus	↓ Pain intensity in rs4411417 T/T and C/T, rs3783641 T/T, and rs752688 C/C ↓ Pain at 90 min in rs4411417 T/T, rs3783541 T/T, and rs7526887 C/C	[17]
CS	Healthy Germans, *n* = 25	*TRPV1*	CAP receptor and transducer of thermal stimuli	rs8065080 (A/G)	Pain/heat detection Patch (infusion) Laser doppler (magnitude)	↑ Pain onset time in AA/AG ↑ Sensitivity to the pain for heat in GG ↓ Heat detection in GG	[18]
CS	Europeans, *n* = 17	*TRPV1*	CAP receptor and transducer of thermal stimuli	rs8065080 (I585V)	Cough sensitivity to CAP Concentration of CAP causing 2 or 5 coughs	↓ Cough sensitivity to CAP in TRPV1-V585	[19]
CS	Healthy Italians, *n* = 20	*TRPV1*	Capsaicin receptor and transducer of thermal stimuli	rs222747 (I315M) rs8065080 (I585V) rs224534 (T469I) rs222749 (P91S)	Cough sensitivity to CAP Unique CAP breaths with dosimeter	↑ Cough sensitivity to CAP in 315 M, 585I, 469I and 91S combined	[20]
CS	Japanese, *n* = 26	*TRPV1*	CAP receptor and transducer of thermal stimuli	2193 (rs460716 C/T), 14727 (C/G), 17775 (rs161385 C/G), 30580 (rs57716901 A/G), 30599 (rs61387317 T/G), and 43524 (rs4790523 T/G)	Burning pain sensitivity Withdrawal latencies from the 48°C hot plate	↑ Burning pain sensitivity in 2193 CT, 14727 CG, 17775 CG, 30580 AG/30599 TG, 43524 TT+TG	[21]
CS	Japanese, *n* = 26	*TRPV1*	CAP receptor and transducer of thermal stimuli	19274 (rs117112057 G/A), 21003 (rs12936340 C/T), 21682 (rs7220415 G/T), 24752 (rs3744686 G/A), 30580 (rs57716901 A/G), 30599 (rs61387317 T/G), 33554 (rs8065080 G/A), 33605 (rs8078936 A/G), 37280 (rs57405156 T/C), 39341 (rs3826503 T/C), and 43524 (rs4790523 T/G)	Capsaicin sensitivity test CAP working solution in mouth in time intervals	Higher oral CAP sensitivity in 19274 GA, 21003 TT/21682 TT/24752 AA, 30580 AA/30599 TT, 33554 GG, 33605 AA, 43524 TT, 37280 TT, and 39341 TT	[21]

Table 1 (continued)

CS	Caucasians, Asians, and African-Americans, $n = 106$	*TAS2R38*	Bitter taste perception	rs713598 (A49P) rs1726866 (V262A) rs102466939 (I296V)	Study design	Population	CAP-impregnated swabs	↑ Bitterness in PAV homozygotes	[22]
CS	Caucasians, Asians, and African-Americans, $n = 106$	*TAS2R3*, *TAS2R4*, and *TAS2R5*	Bitter taste perception	*TAS2R3* (rs765007 C/T), *TAS2R4* (rs2234001 G/C), and *TAS2R5* (rs2234012 A/G and rs2227264 G/T)	CAP-impregnated swabs			↑ Bitterness in CCCAGT diplotype homozygotes	[22]

CAP, capsaicin; SNP, single-nucleotide polymorphisms; CS, cross sectional study.

Gene

Gene function

Polymorphism

Methodology

Results

Discussion

The results of this systematic review evidence the influence of some genetic polymorphisms on CAP tolerance traits, providing a better understanding on the individual preferences in its consumption and its impact on health. These variants were located in or near genes such as *GCH1*, *TRPV1*, *TAS2R38*, *TAS2R3*, *TAS2R4*, and *TAS2R5*, which regulate key biological/physiological processes.

GCH1, a member of the GTP cyclohydrolase family, participates in the enzymatic conversion of GTP into 7,8-dihydroneopterin triphosphate in the biosynthesis of tetrahydrobiopterin (BH4). The main function of BH4 is regulation of monoamine and nitric oxide production, which are implicated in nociceptive signaling [23]. Indeed, alterations in BH4 metabolism have been implicated in several pathological conditions including chronic pain [24]. Indeed, experimental inhibition of BH4 synthesis produces analgesic effects and attenuates neuropathic and inflammatory pain, whereas BH4 administration may exacerbates pain [25]. However, evidence supports that BH4 plays multiple roles in the cardiovascular, immune, nervous and endocrine systems via mitochondrial regulation, energy metabolism, antioxidant resistance of cells against stressful conditions and toxic pathways that may result in cell death, and protection from sustained inflammation, with implications in cardiovascular and metabolic diseases [26, 27].

TRPV1 is a nonselective cation channel, member of the vanilloid TRP family with high expression in sensory neurons, and a significant permeability to large polyvalent cations, calcium, and protons [28]. Although it is activated by numerous stimuli (i.e., heat, voltage, vanilloids, lipids, and protons/cations), CAP-induced TRPV1 intracellular signaling induce the depolarization of nociceptive neurons, leading to action potential firing and ultimately the sensation of spiciness [29]. TRPV1 (known as the specific CAP receptor) plays an essential role in the onset and progression of the burning pain sensation associated with inflammation in peripheral tissues, but it is additionally involved in a wide range of non-pain-related physiological processes including the maintenance of body and cell homeostasis and energy metabolism [30]. Thus, besides involvement in pathological inflammatory conditions, cancer and immunity disorders [31], TRPV1 channel has been also associated to the regulation of aging-associated weight gain and glucose tolerance, being relevant in diabetes prevention and weight control [32].

Furthermore, TAS2R38, TAS2R3, TAS2R4, and TAS2R5 belong to the specific class of G-protein coupled receptors (TAS2Rs or T2Rs) responsible for perceiving bitter taste in mammals [33]. Of note, it has been demonstrated that pure CAP elicit low levels of bitterness in some individuals but not

in others [34, 35]. T2Rs are located in taste buds of the tongue, palate and pharynx lie as well as in extraoral tissues including bronchial smooth muscle and chemosensory cells in gut, where they detect bitter chemicals in foods and other agonist substances [36]. When stimulated by bitter compounds, TA2Rs trigger a transduction cascade resulting in depolarization of the receptor cell and producing a signal conveyed to the central nervous system for sense processing [37]. Variation in bitter taste sensitivity may influence individual preferences for foods with bitter sensory qualities (i.e., cruciferous vegetables) and consequently impact healthstatus [38]. In particular, T2Rs activation can influence ap-petite and body weight control, identifying T2Rs as promising targets for the treatment of obesity [39]. However, it has notbeen suggested that CAP bitterness is a barrier to chili intake, given that the amount of burn is much greater [40].

Obesity management remains an important challenge in clinical care and health systems. Due to beneficial properties on energy balance, CAP administration via supplementation or through chili intake has been postulated as a strategy for obesity control. However, experimental and epidemiological evidence reveal conflicting results, limiting the use of CAP as a potential anti-obesity nutritional therapy. Here, genetic variants affecting CAP tolerance are summarized, which may help to explain the heterogeneity in the effects of CAP on appetite and adiposity outcomes, but also emphasize the need of personalize the consumption of CAP for obesity handling. Moreover, this information provides a better picture in the study of CAP metabolism and contribute to a better understanding of the preferences in its consumption among individuals. However, given limited evidence in humans so far, it is necessary to conduct more clinical studies that explore the anti-obesity effects of CAP and its relationship with the genetic make-up. In addition to SNPs, other structural variants (i.e., genome insertions/deletions, copy number variants, and tandem repeats) need to be further explored for putative associations with CAP metabolism. Furthermore, the analysis of other populations is required, especially in those anciently exposed to CAP trough chili consumption such as Amerindians in Mexico and other Latin American countries with traditional food cultures.

Conclusion

The present systematic review supports the influence of genetic polymorphisms on CAP tolerance by affecting nociceptive signaling, CAP binding, and bitter tasting. This knowledge may facilitate the design of CAP-based nutrigenetic strategies for a more precise clinical obesity approach.

Statement of Ethics

A statement of ethics is not applicable because this study is based exclusively on published literature. Consent to participate statement is not applicable because this study is based exclusively on published literature.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

O.R.-L. conceived the study. O.R.-L. and Y.M.-A. wrote the manuscript. O.R.-L., Y.M.-A., A.A.S.-N., and J.R.C.-M. systematically searched bibliography and critically reviewed the document. All authors approved the final version of the manuscript.

Data Availability Statement

All data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author.

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