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Effect of the curcumin and piperine co-administration on the blood lipid levels and the cardiovascular risk: a systematic review

Efeito da co-administração de curcumina e piperina nos níveis de lipídeos sanguíneos e no risco cardiovascular: uma revisão sistemática

Efecto de la coadministración de curcumina y piperina sobre los niveles de lípidos en sangre y el riesgo cardiovascular: una revisión sistemática

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Mackelly Simionatto
ORCID: https://orcid.org/0000-0002-5445-8696
Universidade Estadual de Ponta Grossa, Brasil
E-mail: mackelly_simionatto@hotmail.com
Katlin Suellen Rech
ORCID: https://orcid.org/0000-0001-6699-2450
Universidade Federal do Paraná, Brasil
E-mail: katlinrech@gmail.com
Mona Lisa Simionatto Gomes
ORCID: https://orcid.org/0000-0001-5179-3985
Centro Universitário Cesumar, Brasil
E-mail: mlgsimionatto@yahoo.com.br
Jane Manfron
ORCID: https://orcid.org/0000-0003-1873-2253
Universidade Estadual de Ponta Grossa, Brasil
E-mail: janemanfron@hotmail.com
Paulo Vitor Farago
ORCID: https://orcid.org/0000-0002-9934-4027
Universidade Estadual de Ponta Grossa, Brasil
E-mail: pvfarago@gmail.com

Abstract
Some plant species show medicinal potential in atherosclerosis and other coronary diseases. Curcumin (CUR) is a yellow-colored phenolic compound from rhizomes of *Curcuma longa* L. that is mainly used as anti-inflammatory, antioxidant, and anticancer. Piperine (PIP) is an alkaloid from the fruits and the seeds of *Piper nigrum* L. and *Piper longum* L. It has several pharmacological activities, including the antioxidant and the immunomodulatory properties. PIP also increases the nutrients absorption. This review aims at investigating the effect of the CUR and PIP co-administration on the lipid profile and the cardiovascular events based on animal and human studies. This study was performed in the main scientific search bases. Among the 4,992 references found, 2,004 papers were initially chosen for the partial reading and 15 of them filled all the selection criteria for the entire reading. The CUR and PIP co-administration generally demonstrated positive effects on lipid profile in animals and humans by reducing total cholesterol, triglycerides, and LP(a) and by increasing HDL-c. In spite of no long-term clinical trial was carried out for investigating the effect of CUR and PIP co-administration on cardiovascular events, the reduction of glucose, AST, and ALP, and the increase of CAT and SOD were recorded as secondary serum markers to avoid the cardiovascular risk. Therefore, the studies usually report that co-administration of CUR and PIP shows efficacy for reducing serum lipids. The effect on preventing cardiovascular events by reducing the cardiovascular risk is lacking of direct evidence.
Keywords: Cardiovascular risk; Dyslipidemia; Phenolic compound; Piperidine alkaloid.

Resumo
Algumas espécies vegetais apresentam potencial medicinal na aterosclerose e outras doenças coronárias. A curcumina (CUR) é um composto fenólico de cor amarela, extraído dos rizomas de *Curcuma longa* L. e utilizado, principalmente, como antiinflamatório, antioxidante e anticâncer. A piperina (PIP) é um alcaloide dos frutos e sementes de *Piper nigrum* L. e *Piper longum* L. Possui diversas atividades farmacológicas, incluindo a antioxidante e as propriedades imunomoduladoras. A PIP também aumenta a absorção de nutrientes. Esta revisão tem como objetivo investigar o efeito da coadministração de CUR e PIP sobre o perfil lipídico e os eventos cardiovasculares, a partir de estudos em animais e humanos. Este trabalho foi conduzido nas principais bases de pesquisas científicas. Dentre as 4.992 referências encontradas, 2.004 artigos foram inicialmente escolhidos para a leitura parcial e 15 deles

preencheram todos os critérios de seleção para a leitura completa. A coadministração de CUR e PIP geralmente demonstrou efeitos positivos no perfil lipídico em animais e humanos, reduzindo o colesterol total, triglicerídeos e LP(a) e aumentando o HDL-c. Apesar de nenhum ensaio clínico de longo prazo ter sido realizado para investigar o efeito da coadministração de CUR e PIP em eventos cardiovasculares, a redução de glicose, AST e ALP e o aumento de CAT e SOD foram registrados como marcadores séricos secundários para evitar o risco cardiovascular. Portanto, os estudos geralmente relatam que a coadministração de CUR e PIP mostra eficácia para reduzir os lipídios séricos. O efeito na prevenção de eventos cardiovasculares pela redução do risco cardiovascular carece de evidências diretas.
Palavras-chave: Alcaloide piperidínico; Composto fenólico; Dislipidemia; Risco cardiovascular.

Resumen

Algunas especies de plantas tienen potencial medicinal en la aterosclerosis y otras enfermedades coronarias. La curcumina (CUR) es un compuesto fenólico de color amarillo, extraído de los rizomas de *Curcuma longa* L. y utilizado principalmente como antiinflamatorio, antioxidante y anticancerígeno. La piperina (PIP) es un alcaloide de los frutos y semillas de *Piper nigrum* L. y *Piper longum* L. Tiene varias actividades farmacológicas, incluidas las propiedades antioxidantes e inmunomoduladoras. PIP también aumenta la absorción de nutrientes. Esta revisión tiene como objetivo investigar el efecto de la coadministración de CUR y PIP sobre el perfil lipídico y los eventos cardiovasculares, a partir de estudios en animales y humanos. Este trabajo se llevó a cabo en las principales bases de investigación científica. Entre las 4.992 referencias encontradas, inicialmente se eligieron 2.004 artículos para lectura parcial y 15 de ellos cumplían todos los criterios de selección para lectura completa. La coadministración de CUR y PIP generalmente demostró efectos positivos sobre el perfil lipídico en animales y humanos, reduciendo el colesterol total, triglicéridos y LP(a) y aumentando el HDL-c. Aunque no se ha realizado ningún ensayo clínico a largo plazo para investigar el efecto de la coadministración de CUR y PIP en eventos cardiovasculares, la reducción de glucosa, AST y ALP y el aumento de CAT y SOD se han registrado como marcadores séricos secundarios para evitar el riesgo cardiovascular. Por lo tanto, los estudios generalmente informan que la coadministración de CUR y PIP muestra eficacia para reducir los lípidos séricos. El efecto sobre la prevención de eventos cardiovasculares al reducir el riesgo cardiovascular carece de evidencia directa.
Palabras clave: Alcaloide de piperidina; Compuesto fenólico; Dislipidemia; Riesgo cardiovascular.

1. Introduction

According to the World Health Organization, two thirds of deaths worldwide are caused by chronic diseases as stroke, cancer, diabetes mellitus (DM), and cardiovascular diseases (CVD) (WHO, 2011). The risk of developing CVD and cancer are impaired by physiological and metabolic changes, caused by obesity, DM, dyslipidemia, systemic arterial hypertension, pro-inflammatory and pro-thrombotic states. These factors are related to the heredity and lifestyle since sedentary lifestyle, stress, alcohol consumption, excessive intake of saturated fats in the diet, besides the continuous use of tobacco may damage the clinical status (Barbalho et al., 2015).

The disruption of lipid metabolism causes the atherosclerosis disease, which involves the dyslipidemia, the chronic inflammation, and the deposition of atherosclerotic plaques in the arterial endothelium (Basatemur et al., 2019). In addition, it is well known that the oxidative stress is highly activated during the atherosclerotic injury (Galkina & Ley, 2009). Atherosclerosis and other coronary diseases affect more than 10% of the world population and are a remarkable concern of health services (GBD, 2018) since cardiovascular problems, such as acute myocardial infarction, stroke, and heart failure may occur over time (Oliveira et al., 2009). Other clinical complication is the liver disorder caused by the inflammatory process related to the particular changes in the lipid metabolism (Dieberger et al., 2018).

Pharmacological and non-pharmacological interventions can be used for treating dyslipidemia and for preventing atherosclerosis and other coronary diseases (Barbalho et al., 2015). In this context, novel studies have been focused on natural products and dietary nutrients for improving the lipid profile (Torres et al., 2015). Curcumin (CUR) is a yellow-colored phenolic compound, chemically known as [1,7-bis(4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione]. CUR is naturally obtained from the rhizomes of *Curcuma longa* L., which are known as turmeric. Turmeric powder containing CUR is widely used as a spice in cooking. CUR demonstrates a high pharmacological potential for interacting with several molecular targets and protein complexes (Nascimento et al., 2012). In particular, CUR reduces the blood lipid levels and has hepatoprotective

effects. These mechanisms are not well elucidated, but includes the reduction in the lipid peroxidases and the 3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMGCoA reductase) (Alwi et al., 2008). In spite of these promising effects on lipid profile, CUR shows photosensitivity and low bioavailability (Rudnik et al., 2020), which hinder its clinical use alone.

Piperine (PIP), 1-(5-[1,3-benzodioxol-5-yl]-1-oxo-2,4-pentadienyl) piperidine, is an alkaloid from the fruits and the seeds of *Piper nigrum* L. and *Piper longum* L. These species are known as black pepper and are widely used as a food spice (Ahmad, 2012). PIP demonstrates anti-inflammatory, antioxidant, immunomodulatory, and anticancer properties. This compound impairs the formation of fat cells, which leads to the blood lipid reduction. The reasonable mechanism to decrease serum lipid levels and obesity occurs by increasing the cholesterol reverse transport via ATP-binding cassette transporter (ABCA1) (Wang et al., 2016). PIP increases the absorption of vitamin A, vitamin B_6, vitamin C, selenium, and beta-carotene (Atal & Bedi, 2010). Despite its pungency, PIP also is used for enhanced the bioavailability of some drugs, including CUR (Duangjai et al., 2013).

Therefore, the co-administration of CUR and PIP seems to be a feasible strategy to increase the bioavailability of CUR and to potentiate their effect on the blood lipids reduction at the same time. Although proposed mechanisms of action were previously reported (Alwi et al., 2008; Atal & Bedi, 2010), preclinical and clinical trials describing the effect of CUR and PIP co-administration on serum lipids and cardiovascular events are restricted (Chakraborty et al., 2017; Hlavačková et al., 2011). In that sense, this systematic review was carried out for collecting secondary data and for providing an evidence synthesis regarding the main research question: Does co-administration of CUR and PIP in a particular dosage improve the lipid profile and have a beneficial effect on cardiovascular events based on human and animal studies?

2. Methodology

This study is a systematic review carried out in accordance with the recommendations of the Cochrane Handbook for Systematic Reviews of Interventions (Higgins et al., 2019). In brief, it is an exploratory-descriptive qualitative research (Gondin & Souza, 2021; Pereira et al., 2018) and it was performed using the guidelines of the Preferred Reporting Items for Systematic Reviews and MetaAnalyzes (PRISMA) (Moher et al., 2009).

2.1 Study selection

The searches were performed in June 2020 using the electronic sites of the following databases: Cochrane (https://www.cochrane.org/), Embase (https://www.elsevier.com/solutions/embase-biomedical-research), Google Scholar (https://scholar.google.com.br/), Lilacs (https://lilacs.bvsalud.org/), Pubmed (https://pubmed.ncbi.nlm.nih.gov/), Scielo (https://scielo.org/), ScienceDirect (https://www.sciencedirect.com/), Scopus (https://www.scopus.com/), and Web of Science (https://www.webofknowledge.com/). The following keywords were searched: curcumin AND piperine AND lipid; curcumin AND piperine AND cholesterol; curcumin AND piperine AND cardiovascular risk. The publication date was not restricted during this process, and documents dated from 1964 to 2020 were achieved. Documents were exported and stored in the EndNote web program. Duplicate documents were deleted using the EndNote tool called “find duplicates”. Duplications which were not excluded in this stage were then removed manually. Partial readings were carried out considering the titles and the abstracts. The complete readings were performed by regarding the full paper content. These research selections were read and analyzed by two reviewers. A third reviewer resolved any selection disagreement between the first two reviewers.

2.2 Exclusion criteria

The following documents were initially excluded from the research files: books, indexes, handbooks, pharmacopoeias, contents, blogs, and papers in languages other than English and Spanish. For the next stage of the study, in which the titles and the abstracts were investigated, the exclusion criteria were: review articles, meta-analysis, papers that evaluated CUR or PIP alone, papers that assessed CUR and PIP with other substance in combination. Studies that did not report data regarding the blood lipid levels or the cardiovascular risk were also deleted.

3. Results and Discussion

The initial search provided a total of 4,992 references. Among them, 2,282 duplications were found and automatically excluded by the use of Endnote. Another 171 papers were manually identified as duplication and excluded. In addition to the papers written in English, documents were also found in Spanish (1), Japanese (5), French (2), Polish (1), and Italian (1).

After excluding books, indexes, handbooks, pharmacopoeias, contents, and blogs, 2,004 files in English involving papers and gray literature remained for reading of their titles and abstracts. Taking into consideration the exclusion criteria, 22 papers were chosen for the complete reading. Five of these documents were then excluded for presenting at least one of the features assumed as exclusion criteria: three papers studied only CUR or PIP alone; one document was excluded because it is a review paper; and a document including CUR, PIP, and other substances was also excluded. Two additional papers were excluded due to the exhausting lack of access. Therefore, 15 papers were chosen for writing this systematic review. These analytical steps are detailed in Figure 1.

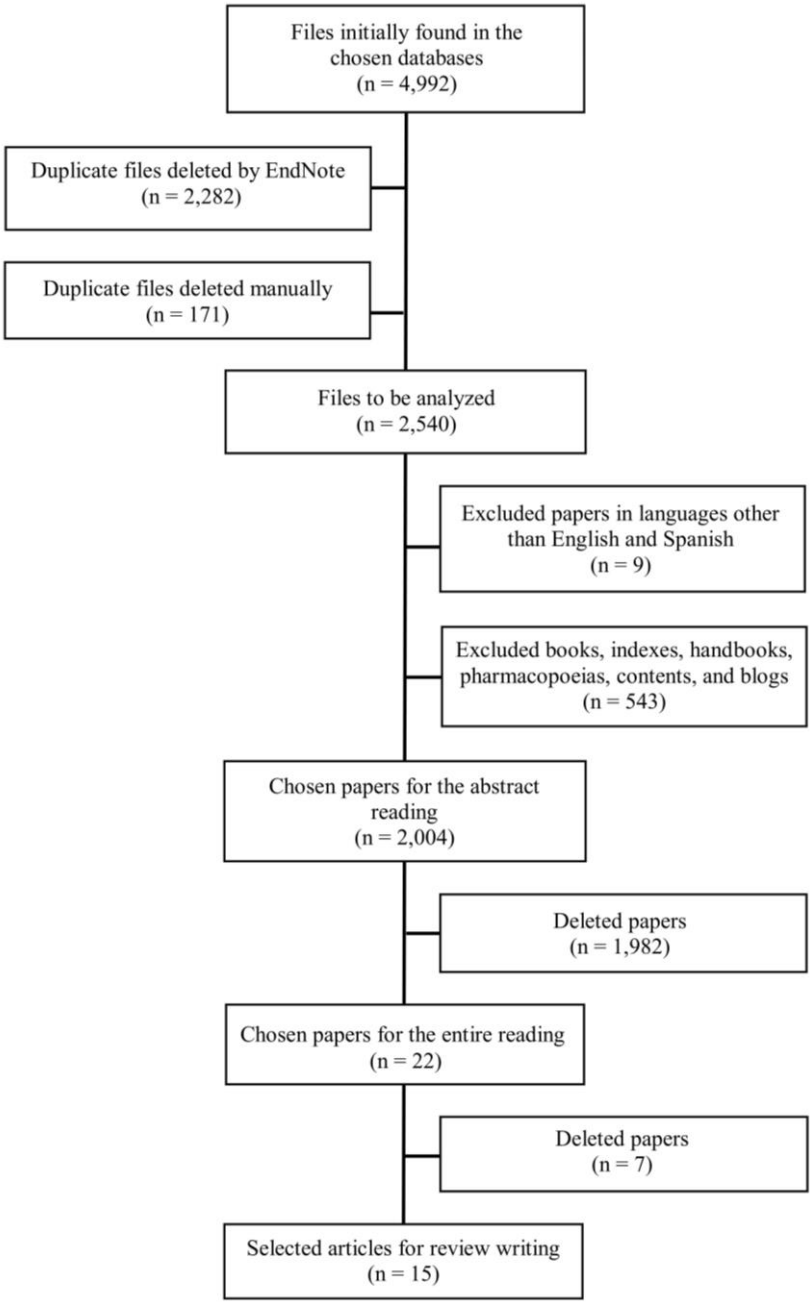
The papers included in the present study refer to animal and human trials regarding to the effect of CUR and PIP co-administration on the blood lipid levels and the cardiovascular risk carried out from 2005 to 2019. Table 1 summarized the analytical data according to the following aspects: aim of the study, country in which the study was performed, tested samples, and observed results. Considering the 15 studies evaluated in full-content structure, 2 of them were carried out in chickens, 7 of them used rats, and 6 of them were performed in humans.

Concerning to the aim of the study, 2 papers reported the CUR and PIP co-administration for improving the chicken performance; 4 of them investigated the antidiabetic effect of these two substances in co-administration; others 2 papers were devoted to study the cardioprotective activity of CUR and PIP; 1 paper aimed at reporting the hepatoprotective effect of CUR and PIP; and others 6 of them investigated the effect of the CUR and PIP co-administration on obese individuals.

Regarding to the country where the studies were carried out, 2 of them involved researchers from Egypt and other 2 papers were performed in China. One paper was written by researches of the following countries: Brazil, India, Slovakia, United States in partnership with Japanese researchers. A total of 7 papers was conducted in Iran, however 6 of them were performed in partnership with researchers from other countries: 1 paper with the United Kingdom; 1 with Australia; 1 with the United States; 1 with the United States and Croatia; and 1 with Mexico. The diversity of countries involved in these studies proves that the CUR and PIP co-administration for providing different pharmacological effects is something of interest worldwide and that the possible biological effects of CUR and PIP, mainly those related to the blood lipid levels and the cardiovascular risk, remain as a question to be answered by science.

Considering the dosage used, a range of doses was reported. CUR was used in a wide range of 25 to 1000 mg/kg/day, while PIP was administrated from 5 to 40 mg/kg/day. These differences can certainly influence the expected pharmacological effects. In addition, a standard dose of CUR and PIP cannot be established for the proposed goals.

Figure 1. Flowchart of the paper selection steps



Note: The paper number is showed in parentheses. Source: Authors.

Table 1. Analysis of chosen papers according to the inclusion criteria that investigated the *in vivo* effect of curcumin and piperine co-administration on the lipid profile and the cardiovascular risk

Paper Aim	Country	Sample(s)	Results	Reference
To check if the curcumin and piperine co-administration in a basal diet can improve the performance and the health status of chickens, including the blood parameters	Egypt	0,5% *Piper nigrum* L. + 0,5% *Curcuma longa* L.	In relation to the control group, the following results were found: ▪ Increase in the chicken weight gain as function of food intake; ▪ Increase in the total protein content (g/dL); ▪ Absence of significant differences in the levels of ALB (g/dL), cholesterol (mg/dL), TG (mg/dL), ALT (U/100 mL), globulin (g/dL), AST (U/100 mL), and ALP (mg/dL); ▪ Reduction in glucose levels (g/dL).	Abou-Elkhair et al., 2014
To verify the effect of a basal diet plus the combination of curcumin and piperine on the performance of chickens, including their blood parameters	Iran	no data	In relation to the control group, the following results were achieved: ▪ No significant differences were recorded in the content of AST (UI/L), ALT (UI/L), LDH (UI/L), LDL-c (mg/dL), HDL-c (mg/dL), TG (mg/dL), total cholesterol (mg/dL), Na^+ (mEg/L), K^+ (mEg/L), and Cl^- (mEg/L).	Akbarian et al., 2012
To investigate the effect of the curcumin and piperine co-administration in a particular yogurt on physiological and biochemical parameters of rats with induced diabetes	Brazil	90 mg/kg curcumin + 20 mg/kg piperine 90 mg/kg curcumin + 40 mg/kg piperine	In relation to the control group, the following results were observed: For the group treated with 90 mg/kg curcumin + 20 mg/kg piperine: ▪ Reduction in blood glucose level (mmol/L), TG (mmol/L), total cholesterol (mmol/L), glucose (mmol/L/24h), urea (mmol/L/24h), and urinary proteins (µmol/L/24h). In addition, decreased serum levels of ALT, AST, ALP (µKat/L), MDA (µmol/L), liver (µmol/L/g tissue), and liver PCO (nmol/mg protein); ▪ HDL-c, GSH-Px (µKat/mg protein), and GSH (mmol/L/g tissue) levels remained unchanged; ▪ Increased levels of SOD (U/mg protein), CAT (µKat/mg protein). For the group treated with 90 mg/kg curcumin + 40 mg/kg piperine: ▪ There were no significant differences in blood glucose level (mmol/L), TG (mmol/L), glycosuria (mmol/L/24h), urea (mmol/L/24h), and urinary proteins (µmol/L/24h); ▪ MDA (µmol/L), liver (µmol/L/g tissue), SOD (U/mg protein), CAT (µKat/mg protein), GSH-Px (µKat/mg protein), GSH (mmol/L/g tissue), and HDL-c remained unchanged; ▪ Reduction in the levels of total cholesterol (mmol/L) and liver PCO (nmol/mg protein); ▪ Increased levels of ALT, AST, and ALP (µKat/L).	Arcaro et al., 2014

To evaluate the efficacy of the curcumin and piperine co-administration against induced cardiotoxicity in rats	India	100 mg/kg curcumin + 20 mg/kg piperine; 50 mg/kg curcumin + 20 mg/kg piperine; 25 mg/kg curcumin + 20 mg/kg piperine	Regarding to the control group, all 3 groups showed: ▪ Improve in the electrocardiographic parameters: heart hate (beats/min), QRS, RR, PR interval (ms), and QT segment (ms); ▪ Reduction of AST, ALT, ALP, CK-MB, CK-NAC, LDH (U/L), total cholesterol, TG (mg/dL), and TBARS (units/mg of protein); ▪ Increased levels of SOD (U/mg protein) and CAT (U/mg protein).	Chakraborty et al., 2017
To study the effect of the curcumin and piperine co-administration on the increase of blood pressure and the aorta remodeling in NO-deficient rats	Slovakia	100 mg/kg/day curcumin + 20 mg/kg/day piperine	In relation to the control group, the following results were recorded: ▪ Decrease in blood pressure only on the 3rd week of treatment; ▪ There was no significant reduction in the aortic wall thickness; ▪ There was a reduction in the levels of PTAH and collagen I; ▪ Increase in actin levels; ▪ No significant differences were observed in the levels of elastin, collagen III, total collagen content, CSA, and Van Gieson.	Hlavačková et al., 2011
To report the effect of curcumin and piperine co-administration on rats subjected to a lithogenic diet	China	500 mg/kg curcumin + 20 mg/kg piperine	In relation to the control group, the following results were achieved: ▪ Reduction in the levels of cholesterol (mmol/L) in serum, TG (mmol/L) in serum, and cholesterol (mmol/L) in bile; ▪ Low change in the levels of phospholipid and bile acid (mmol/L); ▪ 70% reduction in the incidence of cholesterol gallstones; ▪ Decreased liver weight; ▪ Protective effect against lithogenic diet, histopathological changes inhibited; ▪ Reduction in the NPC1L1 and SREBP2 expression.	Li et al., 2015
To analyze the effects of the administration of the combination of Piperine and Curcumin in rats with obesity-induced	USA and Japan	1000 mg/kg curcumin + 50 mg/kg piperine	In relation to the control group, the following results were obtained: ▪ Reduction of the total body fat percentage; ▪ Reduction in the levels of IL-1β and KC/GRO; ▪ There were no statistically significant differences in the levels of IFN-γ, IL-10, IL-12 p70, and IL-6.	Miyazawa et al., 2018
To investigate the effect of curcumin and piperine co-administration on the serum levels of sdLDL-c in obese individuals	Iran and United Kingdom	1000 mg/day curcuminoids + 5 mg/day piperine	In relation to the control group, the following data were observed: ▪ No significant change was found regarding to the serum sdLDL-c content in these individuals.	Moohebati et al., 2014

To evaluate the effect of curcumin and piperine co-administration on the lipid profile of individuals with metabolic syndrome	Iran and Australia	1000 mg/day curcuminoids + 10 mg/day of Bioperine® (extract of *Piper* sp. containing at least 95% piperine)	In relation to the control group, the following results were evidenced: ▪ Reduction in LDL-c, non-HDL-c, total cholesterol, TG, and Lp(a); ▪ Increase in HDL-c; ▪ There was no significant change in sdLDL-c.	Panahi et al., 2014
To report the effect of curcumin and piperine co-administration on oxidative indexes in diabetic individuals	Iran and USA	1000 mg/day curcuminoids + 10 mg/day of piperine	In relation to the control group, the following data were observed: ▪ Increase in total serum antioxidant capacity and SOD activity; ▪ Reduction of MDA activity.	Panahi et al., 2016
To analyze the effect of curcumin and piperine co-administration on the lipid parameters in individuals with type 2 diabetes	Iran, Croatia, and USA	1000 mg/day curcuminoids + 10 mg/day piperine	In relation to the control group, the following results were achieved: ▪ Reduction in serum Lp(a); ▪ Increase in HDL-c; ▪ There was no significant change in the levels of total cholesterol, TG, LDL-c and non-HDL-c.	Panahi et al., 2017
To investigate the effect of curcumin and piperine co-administration on glycemic, hepatic, and inflammatory parameters in individuals with type 2 diabetes	Iran and Mexico	500 mg/day curcuminoids + 5 mg/day piperine	In relation to the control group, the following data were observed: ▪ Reduction in weight (kg) and BMI (kg/m^2); ▪ Reduction in blood glucose level (mg/dL); ▪ Reduction of HbA1c (%), C-peptide (ng/mL), ALT (U/L), and AST (U/L); ▪ There was no significant change in insulin (mIU/L), hs-CRP (g/L), Cr (mg/dL), HOMA-IR, HOMA-β, and HSI.	Panahi et al., 2018
To evaluate the effect of curcumin and piperine co-administration on liver enzymes, lipid profile, glycemic indexes, and disease severity in individuals with nonalcoholic fatty liver disease	Iran and USA	500 mg/day curcuminoids + 5 mg/day piperine	In relation to the control group, the following results were recorded: ▪ Reduction in ALB (g/dL); ▪ There was no significant change in the levels of BIL (mg/dL), TG (mg/dL), HDL-c (mg/dL), ferritin (µg/L), LDH (U/L), FPG (mg/dL), HbA1c (%), BUN (mg/dL), Cr (mg/dL), TSH (mIU/L), WBC (10^9/L), RBC (10^9/L), Plt (10^9/L), ALT (U/L), AST (U/L), ALP (U/L), Hb (g/dL), HCT (%), ESR (mm/hr), Fe (µg/dL), and TIBC (µg/dL); ▪ Significant reduction in the NAFLD severity.	Panahi et al., 2019
To observe the effect of curcumin and piperine co-administration on the lipid profile of normal and hyperlipidemic rats	Egypt	0.1% curcumin + 20 mg/kg piperine 0.25% curcumin + 20 mg/kg piperine 0.5% curcumin + 20 mg/kg piperine	In relation to the control group, the following data were found: ▪ Relative decrease in the mass of liver and heart; ▪ No difference was observed in the body mass gain; ▪ Decreased levels of cholesterol, LDL-c, VLDL-c, TG, and phospholipids; ▪ Increase in HDL-c.	Soliman Ghada, 2005
To detect the	China		In relation to the control group, the	Tu et al., 2014

hypocholestero-lemic effect of curcumin and piperine co-administration on rats subjected to a high-fat diet		100 mg/kg/day curcumin + 5 mg/kg/day piperine	following data were obtained: ▪ Decreased levels of total cholesterol (mmol/L), TG (mmol/L), and LDL-c (mmol/L); ▪ Increase in HDL-c (mmol/L) and ApoA1 (g/L); ▪ No significant change in ApoB (g/L); ▪ Decreased levels of total cholesterol and TG in liver (µmol/g of liver); ▪ Increased levels of total cholesterol, TG, and total bile acid in the stools (µmol/g of stools/day); ▪ Increased activity of LCAT (nmol/h/mL) and CYP7A1 (nmol/h/mg protein).	

Abbreviations:

ALB: albumin; **ALP:** alkaline phosphatase; **ApoAI:** apoliprotein A-1; **ApoB:** apoliprotein B; **ALT:** alanine aminotransferase; **AST:** aspartate aminotransferase; **BIL:** bilirubin; **BMI:** body mass index; **BUN:** blood urea nitrogen; **CAT:** catalase; **Cl^-:** cloreto ion; **CK-MB:** creatine kinase mb fraction, **CK-NAC:** creatine kinase; **Cr:** creatinine; **CSA:** cross sectional área; **CYP7A1:** cholesterol 7α –hydroxylase; **ESR:** erythrocyte sedimentation rate; **FBS:** fasting plasma glucose; **Fe:** iron, **FPG:** fasting plasma glucose; **GRO:** human growth-regulated oncogene; **GSH:** glutathione; **GSH-Px:** glutathione peroxidase activity; **Hb:** hemoglobin; **HbA1c:** glycated hemoglobin; **HCT:** hematocrit; **HDL-c:** high density lipoprotein cholesterol; **HOMA-β:** the homeostasis model assessment-β cell function; **HOMA-IR:** the homeostasis model assessment estimated insulin resistance; **hs-CRP:** high-sensitivity C-reactive protein; **HSI:** hepatic steatotic index; **IFN-γ:** interferon gama; **IL-1β:** interleukin 1 beta; **IL-6:** interleukin 6; **IL-10:** interleukin 10, **IL-12 (p70):** interleukin 12 disulfide-linked heterodimeric 70-kDa cytokine; **K^+:** potassium ion; **KC:** keratinocytes-derived chemokine; **LCAT:** lecithin cholesterol acyltransferase; **LDH:** lactate dehydrogenase; **LDL-c:** low density lipoprotein cholesterol; **Lp (a):** lipoprotein (a); **MDA:** malondialdehyde; **Na^+:** sodium ion; **NAFLD:** nonalcoholic fatty liver disease; **NPC1L1:** Niemann-Pick C1-Like 1 protein; **PCO:** protein carbonyl content **Plt:** platelet; **PR interval:** is the time from the onset of the P wave to the start of the QRS complex on the electrocardiogram; **PTAH:** photungsten acid-hematoxylin staining method; **QRS interval:** waves represent ventricular depolarization; **QT segment:** total duration of ventricular depolarization; **RBC:** red blood cell; **RR interval:** the time elapsed between two successive R waves of the QRS signal on the electrocardiogram; **sdLDL-c:** small dense low density lipoprotein cholesterol; **SOD:** superoxide dismutase; **SREBP2:** sterol regulatory element-binding protein 2; **TAC:** total antioxidant capacity; **TBARS:** thiobarbituric acid reactive substances; **TG:** triglycerides; **TIBC:** total iron-binding capacity; **TSH:** thyroid-stimulating hormone; **UA:** uric acid; **Van Gieson:** Van Gieson staining method; **VLDL-c:** very low density lipoprotein cholesterol; **WBC:** white blood cell. Fonte: Dados da pesquisa (2015).

Regarding to the aim of the study and its main findings, Abou-Elkhair et al. (2014) investigated the effect of using a basal diet plus the CUR and PIP co-administration on the performance and the health status of chickens, including several blood parameters. These phytopharmaceuticals added to the diet increased the ckichen weight and the total protein content, and reduced the glucose level. However, no change occurred in the levels of total cholesterol, triglycerides (TG), aspartate aminotransferase (AST), and alkaline phosphatase (ALP) using *C. longa* extract and *P. nigrum* extract both at 0.5%.

Akbarian et al. (2012) reported a similar study to Abou-Elkhair et al. (2014) using a basal diet plus the CUR and PIP co-administration in chickens, including some additional blood parameters. No significant difference was either observed for lactate dehydrogenase (LDH), low density lipoprotein cholesterol (LDL-c), high density lipoprotein cholesterol (HDL-c), and potassium ion (K^+).

Arcaro and co-authors (2014) studied the effects of an experimental yogurt containing CUR and/or PIP on the biological and biochemical parameters of STZ-diabetic rats. The treatment using CUR at 90 mg/kg and PIP at 20 mg/kg decreased glucose, TG, total cholesterol, AST, ALP, and malondialdehyde (MDA). The levels of HDL-c, glutathione peroxidase (GSH-Px), and glutathione (GSH) remained unchanged. Superoxide dismutase (SOD) and catalase (CAT) presented increased values. When higher amount of PIP (40 mg/kg) was associated with CUR, no additional benefit was achieved. Several mechanisms have been described to explain the antidiabetic activity involving CUR as the stimulation of insulin secretion by pancreatic beta cells, the increasing of muscle tissue, and the loss of body weight by reducing food intake (Best et al., 2007). Other mechanisms have been reported, including the inhibition of hepatic gluconeogenesis and the increased glucose uptake by muscle tissue, which are based on the activation of adenosine monophosphate (AMP)-activated protein kinase (AMPK) by CUR (Ejaz et al., 2009). These indirect effects on blood glucose of CUR show high relevance in this study since DM produces inflammation and excessive availability of energy-rich substrates (glucose and/or free fatty

acids), which increase the production of triglyceride-rich lipoproteins and may lead to a higher cardiovascular risk (Parhofer, 2015). The authors (Arcaro et al., 2014) also detailed that CUR decreased AST, ALP, and MDA, which promote an additive effect since high levels of these enzymes would are related to higher oxidative stress and tissue damage. Unfortunately, these results were statistically similar to those observed for STZ-diabetic rats treated with CUR alone, which represent that PIP did not show any effect on the aforementioned antidiabetic properties and antioxidant activity.

Chakraborty et al. (2017) described that the CUR and PIP co-administration improved some electrocardiographic parameters and presented a significant effect against induced cardiotoxicity. CUR at 50 mg/kg and PIP at 20 mg/kg demonstrated the better results, which were superior to those found for the CUR group. These authors attributed the enhanced effect of these phytopharmaceuticals for three reasons: (a) PIP increased the bioavailability of CUR; (b) CUR and PIP demonstrated antioxidant activity; and (c) CUR also enhanced the nitric oxide (NO) release.

Hlavačková et al. (2018) reported the effect of CUR and PIP at 100 and 20 mg/kg, respectively, on blood pressure and aortic remodeling in NO-deficient rats. The co-administration prevented the increase in blood pressure on 3-week treatment. CUR and PIP also lead to the vascular remodeling and the high elastin level in the blood vessel walls possibly due to the inhibition of matrix metalloproteinase 2 (Banerji et al., 2004). These findings show relevance in this study since atherosclerosis may give rise to acute myocardial infarction and the remodeling of artery vessels can prevent this serious pathologic event.

Li et al. (2015) described the effect of CUR and PIP co-administration on rats subjected to a lithogenic diet. This combination reduced total cholesterol and TG in blood and bile cholesterol. In addition, the gallstone incidence was decreased in 70%. These authors explained these suitable results based on the following rationale: (a) CUR is able to prevent the gallstone formation probably by reducing the expression of the Niemann-Pick C1 like intracellular cholesterol transporter 1 protein (NPC1L1), (b) PIP may increase the CUR bioavailability, and (c) PIP is capable of reducing serum cholesterol levels through its internalization by cholesterol transporting proteins (Duangjai et al., 2013).

Miyazawa et al. (2018) demonstrated the effects of CUR and PIP co-administration obese rats and reported that this combination induced the total body fat loss and the inflammation suppression. According to these authors, these two substances reduces the production of inflammatory cytokines, such as interleukin 1 beta (IL-1β) and keratinocytes-derived chemokine (KC)/human growth-regulated oncogene (GRO) in plasma. However, CUR and PIP did not decrease the expression of interferon gama (IFN-γ), interleukin 10 (IL-10), interleukin 12 disulfide-linked heterodimeric 70-kDa cytokine (IL-12 p70), and interleukin 6 (IL-6). Miyazawa et al. (2018) postulated that the cytokines decrease had no connection to the increase of CUR bioavailability by PIP, but was due to its anti-inflammatory and antioxidant properties, which enhanced the final activity. The authors suggested further studies for clarifying the effect of CUR and PIP co-administration on reducing the oxidative stress.

Moohebati et al. (2014) studied the effect of curcuminoids at 1000 mg/day and PIP at 5 mg/day on the serum levels of LDL-c of obese individuals and observed no significant response. These authors proposed that the cardiovascular effects of curcuminoids might occur by mechanisms that were mainly related to TG levels and did not affect LDL-c subfractions. Moohebati et al. (2014) affirmed the importance of exploring the impact of these substances on serum lipoproteins in more depth.

Panahi et al. (2014) reported the effect of CUR and PIP co-administration on the lipid profile of humans with metabolic syndrome. Reduced values for LDL-c, non-high-density lipoprotein cholesterol (non-HDL-c), total cholesterol, TG and lipoprotein (a) [Lp(a)] were achieved. The increase in HDL-c was also found. Further studies including a high dose and a longer treatment time were suggested. The authors mentioned that several molecular and cellular mechanisms have been described to explain the effect of curcuminoids on lipids, such as the inhibition of lipid biosynthesis by the negative regulation

of lipogenic factors, such as HMG-CoA, sterol regulatory element-binding proteins 1 and/or 2 (SREBP-1/2), and fatty acid synthase. The catabolic stimulus, the biliary excretion of lipids, and the lipid mobilization from adipose tissue (Shin et al., 2011; Zhao et al., 2008) were also involved. Panahi et al. (2014) recommended that an adjuvant therapy using CUR and PIP for a long-lasting treatment could enhance the effect of statins on blood lipid levels.

Panahi et al. (2016) evaluated the CUR and PIP co-administration concerning to the oxidative indices in diabetic individuals. These authors observed an increase in the total serum antioxidant capacity after 12 weeks. The oxidative stress has been involved in harmful damage in type 2 DM patients, which has been led to the long-term complications. In that sense, these substances could be used safely by this particular group due to the antioxidant activity. These authors explained that curcuminoids show phenolic hydroxyl functional groups, which can decrease the NO bioavailability and can protect against reactive intermediates. These compounds can also chelate redox-active metals and can suppress chain reactions that produce radicals induced by metal ions (Baum & Ng, 2004). However, new studies should be further performed to confirm its long-term impact, including at the cardiovascular level.

Panahi et al. (2017) investigated the effect of CUR and PIP co-administration on lipid parameters in DM2 individuals and described their ability to reduce the serum level of Lp(a) and to increase the HDL-c value, while the other lipoproteins did not change. The authors suggested that these phytopharmaceuticals could be used as a dietary supplement for treating dyslipidemia by DM2 patients. Panahi et al. (2017) also discussed that high levels of Lp(a) have been considered an important risk factor for premature atherosclerosis, regardless of LDL-c and non-HDL-c levels. Therefore, the finding that CUR and PIP can decrease Lp(a) in these patients is very clinically relevant (Aguiar et al., 2015; Reiner, 2013).

The CUR and PIP co-administration was also studied regarding the effect on blood glucose, hepatic and inflammatory parameters in DM2 individuals by Panahi et al. (2018). Lower blood glucose, as well as reduced liver parameters were reported. The antidiabetic effect of CUR and PIP was attributed to the hepatic glucose production decrease by the activation of AMPK and the inhibition of glucose-6-phosphatase and phosphoenolpyruvate carboxylase (Fujiwara et al., 2008; Meghana et al., 2007). Curcuminoids can also protect pancreatic islets against oxidative stress, eliminate free radicals and improve the β-cell function (Seo et al, 2008). The current authors suggested again that long-term clinical trials are required to elucidate the anti-diabetic and hepatoprotective properties of CUR and PIP in DM2 patients to verify their effect on vascular complications.

Panahi et al. (2019) investigated the effect of CUR and PIP co-administration on liver enzymes, lipid profile, glycemic indexes, and disease severity in individuals with nonalcoholic fatty liver disease (NAFLD). The results demonstrated the hepatoprotective effect of these natural products in combination by reducing the disease severity due to the inhibition of liver lipogenesis. These data are in agreement with literature since the bile acid metabolism decreased liver steatosis and reversed serum lipid levels abnormalities in mice with NAFLD (Yan et al., 2018). The possible mechanism of action of CUR could be explained by activating AMPK and by inhibiting SREBP-1, which could reduce the hepatic fat accumulation in obese mice and could prevent hepatic steatosis (Um et al., 2013). Another mechanism could be the SREBP-1 expression and the inhibition of SREBP-2 and LDL-c receiver genes (LDL-R), which could restore the lipid storage capacity of hepatic stellate cells and could protect against steatosis and liver fibrosis (Chen & Zheng, 2008; Graham, 2009; Kang & Chen, 2009a; Kang & Chen, 2009b).

Soliman Ghada (2005) described the effect of CUR and PIP co-administration on the lipid profile of normal and hyperlipidemic rats. Decreased levels of cholesterol, LDL-c, very low-density lipoprotein cholesterol (VLDL-c), TG, and phospholipids were recorded. In addition, increased levels of HDL-c were achieved. The aforementioned authors suggested that this drug combination could be used in the treatment of cardiovascular diseases since PIP provided an increased bioavailability for CUR. As supposed mechanisms of action, CUR interfered with the intestinal cholesterol uptake, improved

the cholesterol conversion in bile acids, increased the bile acid excretion, and inhibited lipid peroxidation that led to cholesterol reduction (Patil & Srinivasan, 1971; Soudamini et al., 1992; Sreejayan, 1994).

Tu et al. (2014) studied the hypocholesterolemic effects of CUR and PIP co-administration in rats subjected to a high-fat diet. These phytopharmaceutics were able to decrease serum and hepatic levels of total cholesterol, TG, LDL-c, besides increasing HDL-c levels and fecal levels of total cholesterol, TG, and total bile acid. CUR and PIP regulated the gene expression levels of Apolipoprotein AI (ApoAI), lecithin-cholesterol acyltransferase (LCAT), cholesterol 7 alpha-hydroxylase (CYP7A1), and LDL-R (Yiu et al, 2011). This study demonstrated that the drug co-administration showed high efficacy than CUR alone against hypercaloric diets. Tu et al. (2014) suggested that the mechanism of action involved the increase of cholesterol efflux to the HDL-c particles and of ApoAI and LCAT mRNA levels (Anand et al., 2007; Shoba et al., 1998; Srinivasan, 2007; Suresh & Srinivasan, 2010).

When comparing the results obtained for these 15 studies (Table 1), 6 papers demonstrated that the CUR and PIP co-administration reduced the total cholesterol levels (Arcaro et al., 2014; Chakraborty et al., 2017; Li et al., 2015; Panahi et al., 2014; Soliman Ghada, 2005; Tu et al., 2014), while 2 other papers reported no significant change for this assay parameter (Akbarian et al., 2012; Panahi et al., 2017). Regarding to the TG levels, 6 chosen studies showed the TG reduction (Arcaro et al., 2014; Chakraborty et al., 2017; Li et al., 2015; Panahi et al., 2014; Soliman Ghada, 2005; Tu et al., 2014). No significant difference in the TG levels was observed by Abou-Elkhair et al. (2014), Akbarian et al. (2012), Panahi et al. (2017), and Panahi et al. (2019). One of the CUR and PIP combination tested by Arcaro et al. (2014) also presented no significant difference in TG.

The CUR and PIP co-administration decreased LDL-c levels in 3 papers (Panahi et al., 2014; Soliman Ghada, 2005; Tu et al., 2014), while LDL-c remained unchanged in 4 other studies (Akbarian et al., 2012; Arcaro et al., 2014; Moohebati et al., 2014; Panahi et al., 2017). For HDL-c levels, 4 trials described an increase in this assay parameter (Panahi et al., 2014; Panahi et al., 2017; Soliman Ghada, 2005; Tu et al. 2014), while 3 other papers showed no significant difference when compared with the control group (Akbarian et al., 2012; Arcaro et al., 2014; Panahi et al., 2019). LP(a) was decreased in the studies performed by Panahi et al. (2014) and Panahi et al. (2016). Tu et al. (2014) was the only study that assessed the Apo A1 and Apo B levels, when the CUR and PIP co-administration was used. Apo A1 showed an increase, while Apo B remained unchanged.

Two chosen studied (Chakraborty et al., 2017; Panahi et al., 2018) observed a decrease in AST and ALT values. These parameters remained statistically similar to the control for Akbarian et al. (2012) and Panahi et al. (2019). The drug combination containing lower PIP content tested by Arcaro et al. (2014) reduced AST, ALT, and ALP levels, while the combination containing higher PIP dose led to an increase of these biochemical parameters. A reduction in ALP was reported by Chakraborty et al. (2017). Panahi et al. (2019) described no significant difference for ALP. Two papers demonstrated that the CUR and PIP co-administration reduced the LDH levels (Arcaro et al., 2014; Chakraborty et al., 2017), while 2 other studied reported no significant change for this assay parameter when compared to control (Akbarian et al., 2012; Panahi et al., 2019).

An increase in the CAT and SOD concentration was observed in the studies carried out by Chakraborty et al. (2017) and Arcaro et al. (2014), when lower PIP amount was used. SOD was also measured by Panahi et al. (2016), who reported an increase in its level. Panahi et al. (2017) observed a reduction in the MDA levels, as well as Arcaro et al. (2014) at lower PIP concentration. A decrease in blood glucose levels were recorded in 2 papers (Arcaro et al., 2014; Panahi et al., 2018).

In brief, the CUR and PIP co-administration generally demonstrated positive effects on lipid profile in animals and humans by reducing total cholesterol, triglycerides, and LP(a) and by increasing HDL-C. In spite of no long-term clinical trial

was carried out for investigating the effect of CUR and PIP co-administration on cardiovascular events, the reduction of glucose, AST, and ALP, and the increase of CAT and SOD were recorded as secondary serum markers to avoid the cardiovascular risk. No particular dose was used as a standard. Therefore, the studies usually report that co-administration of CUR and PIP at different doses shows efficacy for reducing serum lipids. The effect on preventing cardiovascular events by reducing the cardiovascular risk is lacking of direct evidence.

The differences observed in the aforementioned clinical trials may be due to the heterogeneity of the studies, since diverse dosages of CUR and PIP were reported. In addition, different animal species or human groups, time intervals, and matrices as yogurt were also used, besides the phytopharmaceutical composition was varied since the curcuminoids were described in some papers. Hence, these was some confounding factors that hinder the question analysis as outlined. Therefore, it is recommended to perform a meta-analysis study in order to facilitate the data understanding, to compare the obtained results more accurately by suitable statistical techniques, and to draw more reliable conclusions or even new information (Egger & Smith, 1997; Filho et al., 2014). In addition to the meta-analysis, further long-lasting clinical trials with appropriate standard parameters must be performed in order to evidently ensure the effect of CUR and PIP co-administration on the lipid profile and the cardiovascular risk.

Piyachaturawat et al. (1983) who reported histopathological changes in rats described the PIP toxicity in doses ranging from 100 to 500 mg/kg. Thus, its long-term use should be more widely investigated. Burgos-Morón et al. (2010) sent a letter to the International Journal of Cancer reporting that the CUR and PIP co-administration may present some negative effects. In this document, the authors described that PIP have been usually used in order to increase the CUR levels in the biological tissues. However, they reported that PIP has been described as a drug inhibitor of the cytochrome P450 metabolism and may cause toxicity in people who are using certain medications. Besides, they recorded some reports that demonstrated the CUR toxicity in certain situations. Thus, Burgos-Morón et al. (2010) suggested that a risk-benefit profile should be established for the safety use of CUR and PIP.

4. Conclusion

According to the chosen studies, different CUR and PIP combinations have been investigated in experimental models in order to evaluate the effect on the lipid profile and the reduction of cardiovascular risk. It was observed that the concentrations of 100, 500, and 1000 mg/kg/day for CUR, and 5, 10, and 20 mg/kg/day for PIP were widely used.

The CUR and PIP co-administration usually demonstrated positive effects on lipid profile in clinical studies involving animals and humans by reducing total cholesterol, triglycerides, and LP(a) and by increasing HDL-C. In spite of no long-term clinical trial was performed for evaluating the effect of CUR and PIP co-administration on cardiovascular events, the reduction of glucose, AST, and ALP, and the increase of CAT and SOD were recognized as secondary serum markers to circumvent the cardiovascular risk. Therefore, a meta-analysis or further standardized long-lasting clinical trial should be performed.

In summary, the studies generally report that co-administration of CUR and PIP at different doses shows certain efficacy for reducing serum lipids. The effect on preventing cardiovascular events by reducing the cardiovascular risk is lacking of direct evidence. Safety and toxicology issue remain unknown.

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