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Health benefits, extraction and development of functional foods with curcuminoids

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ABSTRACT

Turmeric (*Curcuma longa*) is an important condiment used in the culinary of several countries to spice and give a more intense yellow color to food. The importance of this root has gained more attention due to the presence of bioactive compounds known as curcuminoids (the main class of phenolic compounds found in turmeric). The health benefits attributed to curcuminoids are mainly linked to curcumin, the major compound among curcuminoids. Scientific evidence from pre-clinical and clinical trials indicate that turmeric extracts (rich in curcumin) and curcumin can effectively improve the status of subjects by reducing the risk of cardiovascular diseases and diabetes as well as assisting in the management of illness. The present review aims to highlight the use of green extraction technologies to obtain curcuminoid-rich extracts and the health benefits associated with the consumption of turmeric extracts and curcumin (as dietary supplements) against cardiovascular diseases, diabetes, metabolic syndrome, arthritis, and mental disorders at clinical trial level. The current knowledge about the development of functional foods with curcumin is also discussed.

1. Introduction

Non-communicable diseases (cardiovascular diseases, diabetes, metabolic syndrome, arthritis, and mental disorders, for example) can drastically affect the wellbeing of general population and are the leading cause of deaths worldwide. In this sense, reducing the risk and improving the management of non-communicable diseases are key strategies to reduce the number of death and health-care costs (World Health Organization, 2011, 2018). Natural alternatives, especially functional foods have been seen as interesting options to assist in the management of several diseases. Functional foods have a specific purpose: provide a healthy benefit from its consumption, which can be derived from the presence of bioactive compounds. Reducing or replacing fat and salt, including a cholesterol lowering component or producing foods with a probiotic microorganism are some of the most relevant strategies used to produce this category of food products (Granato et al., 2020).

Curcuminoids are phenolic compounds found in the roots of turmeric (*Curcuma longa*), a perennial plant from the *Zingiberaceae* family. These compounds are responsible for the appreciated color (between orange and yellow) of the condiment produced from this root. This native plant of India is currently largely cultivated in locations characterized by warm and wet tropical climate in Asia such as Indonesia and China. In traditional cuisine, turmeric has been used as a spicy ingredient as well as yellow pigment (Meng et al., 2018).

In order to understand and use curcuminoids in the production of functional foods, the selection of appropriate extraction conditions play a central role to obtain extracts and preserve the biological activity of extracts. However, this class of compounds is characterized by its poor solubility in water, which imposes an important challenge for researchers and professionals of the food industry (Euterpio, Cavaliere, Capriotti, & Crescenzi, 2011; Sahne, Mohammadi, Najafpour, & Moghadamnia, 2016; Shirsath et al., 2017). Green extraction technologies can be of great value to extract these bioactive compounds without the use of toxic solvents, reduce extraction time, are suitable for thermolabile compounds, and also have reduced environmental (Ameer,

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Shahbaz, & Kwon, 2017; Putnik et al., 2018; Žlabur et al., 2020).

The biological effect related to curcuminoids was characterized (in terms of molecular targets and physiological effects at animal level) against some of the main global diseases such as cardiovascular diseases, diabetes, metabolic syndrome and arthritis. The protective effect derived from these compounds involve multiple mechanisms. For instance, curcumin has been associated with improved homeostasis, enhanced vascular function, anti-inflammatory activity, antioxidant activity, and improving the bioavailability of nitric oxide that can improve the protection of the cardiovascular system against atherosclerosis and related diseases (Campbell & Fleenor, 2018). Similar supporting scientific evidence has also been found for diabetes. The protection of pancreatic cells dedicated to production of insulin as well as reducing insulin resistance in animal models, which are relevant to reduce the risk of developing and manage type 2 diabetes (Pivari, Mingione, Brasacchio, & Soldati, 2019).

The study of the biological effects of turmeric extracts and curcumin in healthy population and subjects diagnosed with non-communicable diseases is an important step towards the development of functional by providing stronger evidence about their health benefits (in relation *in vitro* and animal studies). Thus, this review aims to highlight the role of green extraction technologies to obtain extracts rich in curcuminoids, the effect of turmeric extracts and curcumin in the protection against and/or management of cardiovascular diseases, diabetes, metabolic syndrome, and arthritis at clinical level, and also the application as functional ingredient.

2. Composition and bioactive compounds

In terms of chemical composition, turmeric is a root that is predominately composed of water (80–90%), followed by carbohydrates (around 13%), proteins (2%), minerals (2%) and lipids (<1%) (Hirun, Utama-ang, & Roach, 2014; Kuttigounder, Lingamallu, & Bhattacharya, 2011). Among the minor components of turmeric, curcuminoids have a central role and may compose up to 10% of dry turmeric powder (Shelake, Yadav, Jadhav, & Dabhi, 2018; Thangavel & Dhivya, 2019). This category is mainly composed of curcumin, demethoxycurcumin, and bisdemethoxycurcumin that can compose 62–90, 9–23, and 0.3–14 mg/g of commercial turmeric products (extracts and powders), respectively (Peram, Jalalpure, Joshi, Palkar, & Diwan, 2017). Additionally, more than 50 curcuminoids (such as bisabocurcumin, curcumalongin, cyclocurcumin, and terpecurcumin) have been identified in turmeric (Meng et al., 2018).

3. Extraction of bioactive compounds from turmeric

Obtaining curcuminoid-rich extracts is an important stage to maximize the further application in foods. In this sense, many studies have been carried out to evaluate the influence of conventional and emerging extracting technologies (Table 1). Curcumin have a central role among the bioactive compounds found in turmeric and comprises between 1 and 7% of the root (Euterpio et al., 2011; Sahne et al., 2016; Shirsath et al., 2017). In terms of conventional solvent extraction, the recovery of curcumin was reported to reach 69.1% using a 70% hydroethanolic solution (Paulucci, Couto, Teixeira, & Freitas, 2013).

Due to the poor solubility in water, the extraction of curcumin requires the use of organic solvents. In this context, solvent composition plays a central role to improve the extraction yield and favors the use of solvent such as ethanol and acetone (Priyadarsini, 2014). In terms of strategy to separate curcumin from turmeric, the continuous extraction carried out in Soxhlet can be indicated as a first approach to improve the recovery of curcumin (1.3 and 6.9 g curcumin/100 g) from turmeric (Euterpio et al., 2011; Sahne et al., 2016; Shirsath et al., 2017; Wakte et al., 2011).

In order to improve the efficiency of curcumin extraction, studies have been performed with emerging and green technologies such as

Table 1
Extraction of bioactive compounds from turmeric.

Technology	Extraction conditions	Recovery efficiency/ curcumin content and *optimum conditions*	Ref
Conventional solvent extraction	Solid/solvent ratio: 1:4 and 1:6 g/g; time: 12 and 24 h; agitation: 30 and 70 rpm; temperature: 50 and 80 °C; solvent: 70 and 96% hydroethanolic solution	RE: 69.1%, *1:6 g/g, 12 h, 30 rpm, 80 °C, and 70% hydroethanolic solution*	(Paulucci et al., 2013)
Soxhlet extraction	Sample amount: 15 g; temperature: 60 °C; time: 8 h; and solvent: acetone	CC: 6.9 g curcumin/ 100 g sample	(Sahne et al., 2016)
Soxhlet extraction	Sample amount: 10 g; solvent volume: 250 mL; solvent: ethanol; time: 8 h; and temperature: 78 °C	CC: 1.3 g curcumin/ 100 g sample	(Shirsath et al., 2017)
Soxhlet extraction	Solid/solvent ratio: 1:100 g/mL; time: 8 h/day for 3 days, and solvent: acetone	CC: 1.35 g curcumin/100 g sample	(Euterpio et al., 2011)
Ultrasound-assisted extraction	Solid/solvent ratio: 1:20 g/mL; solvent: acetone; power: 90 W; time: 10–40 min; and temperature: 25–40 °C	CC: 3.9 g curcumin/ 100 g sample, *35 °C, 30* min	(Sahne et al., 2016)
Ultrasound-assisted extraction	Solid/solvent ratio: 1:3 g/L; solvent: ethanol or acetone (soaking and extraction); and time: 5 min	RE: 71.4%, *water as soaking solvent followed by ethanol as extracting solvent, and 5* min	(Wakte et al., 2011)
Ultrasound-assisted extraction	Solid/solvent ratio: 1:15–1:55; time: up to 1 h; solvent: ethanol, methanol, acetone, and ethyl acetate; particle size: 0.09, 0.10, 0.21 and 0.85 mm; temperature: 25–55 °C; frequency: 22 and 40 kHz; and power: 250 W	RE: 72%, *1:25, 1 h, ethanol, 0.09 mm, 35 °C, 22 kHz, and 250 W*	(Shirsath et al., 2017)
Microwave-assisted extraction	Solid/solvent ratio: 1:20 g/mL; solvent: acetone; power: 100–450 W; and time: 0.5–3 min	CC: 2.4 g curcumin/ 100 g sample, *2 min, and 100 W*	(Sahne et al., 2016)
Microwave-assisted extraction	Solid/solvent ratio: 1:3 g/L; solvent: ethanol, acetone, water; time: 1–7 min; and power: 140 W	RE: 90.7%, *water as soaking solvent followed by acetone as extracting solvent, and 5* min	(Wakte et al., 2011)
Subcritical water extraction	Sample amount: 0.1 g; flow rate: 0.5 mL/ min; 5.0 MPa; temperature: 180, 200 and 220 °C; and pH: 1, 1.5, and 2	CC: 1.35 g curcumin/100 g sample, *197 °C, 62 g/L buffer at* pH *1.6*	(Euterpio et al., 2011)
Subcritical water extraction	Flow rate: 1, 2.5, and 4 mL/min; temperature: 90, 120, and 150 °C; and particle size: 0.5, 1 and 1.5 mm	RE: 90.2%, 150 °C, *1 mL/min, and 0.5 mm*	(Mottahedin et al., 2017)
Subcritical water extraction	Particle size: 0.6, 0.71, 1, and 2 mm; temperature: 120–160 °C; time: 6, 10, 14, 18 and 22 min;	RE: 76.0%, *1 MPa, 140 °C, 0.71 mm, and 14* min	(Kiamahalleh et al., 2016)

(*continued on next page*)

Table 1 (*continued*)

Technology	Extraction conditions	Recovery efficiency/ curcumin content and *optimum conditions*	Ref
	and pressure: 1, 1.5, 2, and 2.5 MPa		
SC-CO_2	Sample amount: 10 g, time: 240 min; pressure: 30 MPa; temperature: 50 °C; flow rate 5 mL/min; co-solvent: ethanol; and co-solvent proportion: 10%	RE: 69.4%	(Wakte et al., 2011)

CC: curcumin content (g curcumin/100 g sample), RE: recovery efficiency (% of total curcumin, w/w), RT: room temperature, andSC-CO_2: supercritical CO_2.

ultrasound (US), microwave (MW), subcritical water, and supercritical CO_2 extraction (SC-CO_2). The main advantages of these technologies are related to reduction in the time of extraction, energy consumption and residues generated (Chemat et al., 2020). Regarding the effect of US, the study carried out by Sahne et al. (2016) indicated that the use of this technology provided extracts with curcumin content (3.9 g curcumin/100 g sample) in the range of values observed for Soxhlet, as indicated above. However, it is important to consider the effect of other extraction variables such as solvent composition, solid/solvent ratio, extraction time, particle size, temperature, and US frequency as indicated in the studies performed by Wakte et al. (2011) and Shirsath et al. (2017).

In a similar way to US, MW can be applied to obtain curcumin-rich extracts. For instance, the quantification of curcumin in a extract obtained using a MW (2.4 g curcumin/100 g sample, after 2 min of irradiation) was in the range observed for Soxhlet, as indicated above (Sahne et al., 2016). In terms of recovery efficiency, the study carried out by Wakte et al. (2011) indicated high recovery values (90.7%) when irradiated for 5 min (as a pre-treatment for extraction with acetone).

In the case of subcritical water extraction, Euterpio et al. (2011) indicated that this technology could be used to extract curcumin (1.35 curcumin/100 g sample). The authors also highlighted the importance of selecting appropriate extracting conditions to improve the extraction efficiency such as reducing the pH of water to 1.6 and increasing the temperature to 197 °C. Likewise, other experiments with subcritical water extraction also reported high recovery yields of curcumin (between 76.0 and 90.6%) (Kiamahalleh, Najafpour-Darzi, Rahimnejad, Moghadamnia, & Kiamahalleh, 2016; Mottahedin, Haghighi Asl, & Khajenoori, 2017). Regarding the effect of SC-CO_2 in the extraction of curcumin, Wakte et al. (2011) obtained a recovery efficiency of 69.4% using ethanol as co-solvent and keeping the temperature at 50 °C during extraction.

Taking into account these technologies and approaches to extract curcumin from turmeric, seems reasonable to consider that both conventional and emerging technologies can be used to obtain curcumin-rich extracts. Considering the long extraction periods to obtain the extracts using conventional technologies (agitation and Soxhlet) and the use of organic solvents (especially acetone), the use of alternative technologies and approaches that produce extracts using less harmful and toxic solvent in a shorter period of time can be of great value to enhance the use of curcumin in scientific studies and commercial applications in food and pharmaceutical areas.

4. Health benefits

This section is comprised of studies that explored the effect of turmeric extract and curcumin in the form of dietary supplements (such as tablets) in both healthy and subjects diagnosed with non-communicable diseases. A schematic representation of the mechanisms of action of curcuminoids on disease prevention is presented in Fig. 1.

4.1. Cardiovascular diseases

The cardiovascular diseases are the leading cause of death among the non-communicable diseases at global scale (World Health Organization. (2018) (2018), 2018). This concerning scenario have been associated with many risk factors such as dyslipidemia, high blood pressure, elevated pro-thrombotic factors, reduced or lack of physical activity, high levels of homocysteine, obesity, tobacco consumption, as well as psychological conditions such as stress and depression (Yusuf, Reddy, Ôunpuu, & Anand, 2001). In order to reduce the risk of developing cardiovascular diseases, a better management or avoidance of these aforementioned habits are necessary for both healthy and people in the high-risk group (Stewart, Manmathan, & Wilkinson, 2017; World Health Organization. (2018) (2018), 2018).

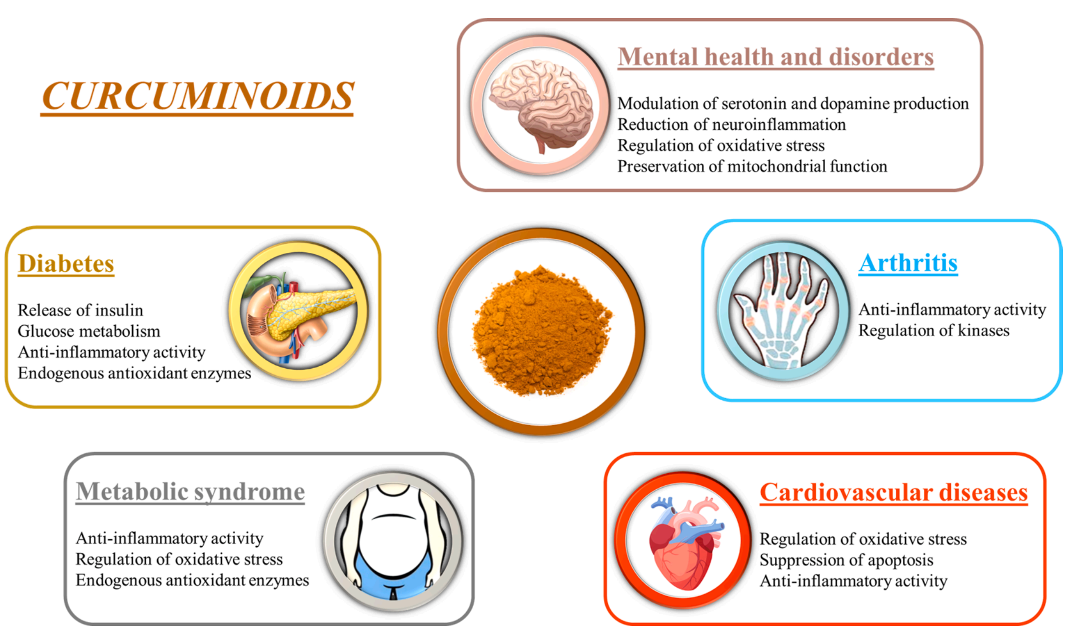

Fig. 1. Mechanisms of action of curcuminoids on disease prevention.

The mechanisms of action of curcuminoids involved in the protection against cardiovascular diseases comprise the regulation of oxidative stress, suppression of apoptosis (programmed cell death) and anti-inflammatory activity. In terms of oxidative stress, previous studies reported that curcuminoids can induce the activity of endogenous antioxidant enzymes, delay the formation of reactive oxygen species, and preserve mitochondrial redox potential and function (Correa et al., 2013; Yang, Wu, Li, & You, 2013; Yang, Duan, et al., 2013). Regarding the suppression of apoptosis, curcuminoids were associated with enhanced expression of B-cell lymphoma 2 (Bcl-2) in myocytes as well as suppressing silent information regulation 1, Bcl-2/adenovirus E1B 19 kDa interacting protein 3, beclin-1, caspase activity, and Bcl-2-associated X protein (He et al., 2018; Huang et al., 2015). In the case of anti-inflammatory potential of curcuminoids, the inhibitory activity in the expression of genes associated with leukocyte adhesion and transendothelial migration was indicated as relevant effect to improve the protection against cardiovascular diseases (Coban et al., 2012). Furthermore, scientific evidence indicates meaningful improvements in the cardiovascular status of by healthy subjects and patients with coronary artery disease or risk factors (Table 2).

Regarding the effect of turmeric extracts and curcumin consumption in healthy subjects (female and male, from 19 to 74 years, and without history of cardiovascular diseases), a recent study indicated that the daily consumption during 12 weeks was associated with higher flow-mediated dilation in brachial artery and bioavailability of vascular nitric oxide (Santos-Parker et al., 2017). Furthermore, the authors also observed a significant reduction in the oxidative stress related to endothelium-dependent dilation. In the same line of thought, another study indicated that flow-mediated dilation was improved but only when a dose of 200 mg of CurcuWIN® (a commercial product with 20–28% of turmeric extract) was consumed for 8 weeks (Oliver et al., 2016).

An improvement in the blood-related risk factors was also associated with regular consumption of curcumin (80 mg curcumin, Longvida® commercial product) for 4 weeks (DiSilvestro, Joseph, Zhao, & Bomser, 2012). In this case, the blood levels of alanine amino transferase, total triglycerides, and soluble intercellular adhesion molecules were reduced. Additionally, the supplemented group also displayed higher levels of catalase and nitric oxide level than the placebo one. However, the activity of myeloperoxidase (an enzyme that produces radical species) was increased in the supplemented group. Another related outcome was reported for the daily consumption of 150 mg curcumin for 8 weeks in combination of regular exercise in postmenopausal women (Akazawa et al., 2013). The subjects in the groups with supplemented and exercising groups displayed enhanced carotid arterial compliance due to regular exercise in comparison to placebo and sedentary groups.

The consumption of turmeric extract or curcumin was also associated with improved health status in patients displaying risk factors related to cardiovascular diseases. For instance, subjects with coronary artery disease that consumed 500 mg curcumin/d for 2 months displayed lower blood levels of total cholesterol, HDL-cholesterol and high sensitive C-reactive protein (hs-CRP) levels than the patients in placebo group at the end of trial (Mirzabeigi et al., 2015). Similarly, Shao, Jia, Li, and Li (2017) indicated significant improvements in the patients with Takayasu arteritis (an inflammation characterized by the formation of granules in the aorta and main ramifications vessels) after the supplementation of curcumin (300 mg curcumin/d for 4 weeks). According to the authors, the patients in the supplemented group showed lower scores in the Birmingham Vascular Activity score (BVAS) as well as reduced levels of tumor necrosis factor-α, CRP, and erythrocyte sedimentation rate (ESR).

Turmeric extract and curcumin can also improve the health status of obese people. The study carried out by Campbell and Ouyang (2019) indicated significant reduction of homocysteine and HDL blood levels whereas the other blood indicators were not affected. The subjects of this study consumed 193 mg curcuminoids/d for 12 weeks. A similar outcome was reported in a study with obese people that consumed 193 mg curcuminoids/day for 30 days (Mohammadi et al., 2013). It is also relevant to mention that another study with chronic smokers also support the health benefits associated with the consumption of curcumin (Barber-Chamoux et al., 2018). In this case, the flow-mediated dilation was improved in females and subjects that had low risk of developing cardiovascular disease.

4.2. Diabetes

Diabetes is a cluster of diseases that causes hyperglycemia on individuals due to inadequate secretion and/or action of insulin. The

Table 2
Effect of turmeric extract and curcumin in subjects at risk of cardiovascular diseases and diagnosed subjects.

Subjects characteristics	Experimental conditions	Study characteristics	Effect	Ref
F and M, 45-74 y, 39 healthy subjects	400 mg curcumin/d for 12 weeks	R, Pc, and Db	↑ Brachial artery flow-mediated dilation and vascular nitric oxide bioavailability ↓ Oxidative stress related to endothelium-dependent dilation	(Santos-Parker et al., 2017)
F and M, 19–29 y, healthy subjects, compliance > 80%	50 and 200 mg CurcuWIN®/d for 8 weeks	R, Pc, and Db	↑ Flow-mediated dilation with 200 mg dose	(Oliver et al., 2016)
F and M, 40–60 y, 38 healthy subjects	80 mg curcumin/d for 4 weeks	R and Pc	↑ Catalase and myeloperoxidase activity and nitric oxide levels ↓ Alanine amino transferase activity and triglyceride and soluble intercellular adhesion molecule levels	(DiSilvestro et al., 2012)
F, 58–60 y, 51 healthy postmenopausal subjects	150 mg curcumin/d for 8 weeks With exercise	R and Pc	↑ Carotid arterial compliance with exercise	(Akazawa et al., 2013)
F and M, >18 y, 33 coronary artery disease subjects	500 mg curcumin/d for 2 months	R, Pc, and Db	↓ Total cholesterol, HDL-cholesterol, and hs-CRP	(Mirzabeigi et al., 2015)
F and M, 19–52 y, 246 subjects with Takayasu arteritis	300 mg curcumin/d for 4 weeks	R, Pc and Db	↓ BVAS, NF-α, CRP, and ESR	(Shao et al., 2017)
M, 18–35 y, 22 obese subjects	193 mg curcuminoids/d for 12 weeks	R, Pc, and Db	↑ HDL level ↓ Homocysteine level	(Campbell & Ouyang, 2019)
F and M, 18–52 y, 30 obese subjects	500 mg curcuminoids/d for 30 days	R, Pc, Db, and Co	↓ Total triglycerides level	(Mohammadi et al., 2013)
F and M, 50–70 y, 18 chronic smokers	5 g curcumin (single dose), samples taken after 2 h	R, Pc, Db and Co	↑ Flow-mediated dilation in females and subjects with low risk of cardiovascular disease	(Barber-Chamoux et al., 2018)

Subject characteristics: Female/Male, age, number of subjects; Experimental conditions: dose and experimental period; Study characteristics: R: randomized, Pc: Placebo controlled, Dd: Double-blind, and Co: Cross-over; BVAS: Birmingham Vascular Activity Score; hs-CRP: high-sensitive C-reactive protein levels; ESR: Erythrocyte Sedimentation Rate; HDL: high density lipoproteins; and NF-α: Tumor necrosis factor-α.

carriers of these diseases can be grouped in four categories: type 1 (low to none insulin production associated with insulin dependency to survive); type 2 (reduced insulin production associated with insulin dependency for management); gestational diabetes (diagnosed in the second or third trimester with similar characteristics to type 2 diabetes); and other causes (due to kidney diseases, induced by drug treatments, and diabetic syndrome with similar characteristics to type 2 diabetes) (American Diabetes Association, 2019; Centers for Disease Control & Prevention, 2020).

The risk factors for diabetes include history of symptomatic relatives (first degree), some ethnicities (Latino, African American, and Pacific Islander, for instance), preexisting physiological and metabolic conditions (such as hypertension and dyslipidemia) and history of cardiovascular disease, polycystic ovary syndrome, sedentarism, and obesity. In the case of inadequate management, diabetes can cause life-long severe effects and eventual lead to failure of kidneys, blood vessels, heart, and eyes (American Diabetes Association, 2014, 2019).

Insulin resistance is another important indicator that can indicate a potential evolution from normoglycemia towards hyperglycemia, which is known as prediabetes. In other words, the individual does not fit in the criteria for diabetes diagnosis but the blood glucose level is higher than normal (≥126 mg/dL). This condition is characterized by the combination of reduced sensibility to insulin with a higher production and secretion of insulin. This condition can be reversed by changing habits, especially regarding the lifestyle, diet, physical activity, and staying motivated (American Diabetes Association, 2014; Centers for Disease Control & Prevention, 2020).

The main mechanisms that explain the role of curcuminoids in the management of diabetes are related to glucose metabolism, anti-inflammatory activity, regulation of oxidative stress, and related pathways. For instance, curcuminoids can present hypo-glycemic effect and ameliorate insulin resistance in skeletal muscle by inducing the activity of glucose transporter 4 system and the level of insulin receptor substrate 1, which increase the absorption of glucose (El-Moselhy, Taye, Sharkawi, El-Sisi, & Ahmed, 2011; Maithilikarpagaselvi, Sridhar, Swaminathan, & Zachariah, 2016; Na et al., 2011). These natural polyphenols can also inhibit the essential gluconeogenesis enzymes (phosphoenolpyruvate carboxykinase and glucose-6-phosphatase) (Kim, Davis, Zhang, He, & Mathews, 2009). Moreover, inducing the activity of endogenous antioxidant enzymes and reduce plasma lipid peroxidation is another mechanism attributed to curcuminoids (Gutierres et al., 2019).

Curcuminoids also display anti-inflammatory activity by increasing the levels of adipokine adiponectin and stress response proteins (heat shock proteins 70 and 90 and Sirtuin 1) as well as reducing inflammatory intermediate molecules such as interleukins (IL) and monocyte chemoattractant protein 1 (Gonzales & Orlando, 2008; Weisberg, Leibel, & Tortoriello, 2008). Additionally, curcumin downregulated the expression of cyclic nucleotide phosphodiesterases, which can facilitate the secretion of insulin from pancreatic β-cells (Rouse, Younès, & Egan, 2014).

The consumption of turmeric extract or curcumin have been showing promising results to assist in the management of diabetes and individuals in the risk group (Table 3). In the case of individuals in the risk group with polycystic ovarian syndrome, a recent study indicated that the daily consumption of 500 mg curcumin for 12 weeks induced an increase in insulin sensitivity, HDL levels, and in the expression of peroxisome proliferator-activated receptor gamma (PPAR-γ) and low-density lipoprotein receptor (LDLR). Moreover, the authors also obtained significant reduction in body weight as well as cholesterol, LDL, fasting glucose and serum insulin levels in the curcumin supplemented group in comparison to subjects in placebo group (Jamilian et al., 2020). In a similar way, Sohaei, Amani, Tarrahi, and Ghasemi-Tehrani (2019) obtained a significant reduction in insulin levels after supplementing the diet of polycystic ovarian syndrome subjects with 500 mg curcumin/day for 6 weeks. Other related experiment indicated that curcumin supplementation (1500 mg curcumin/day for 12 weeks) increased the expression of peroxisome proliferator activated receptor γ coactivator 1α (PGC1α) and glutathione peroxidase (Gpx) expression (Heshmati et al., 2020). This effect is an important outcome to enhance the antioxidant defense against the oxidative damage associated with polycystic ovarian syndrome.

The enhancement on healthy status of diabetic subjects was also reported after the consumption of turmeric extracts or curcumin. For instance, Shafabakhsh et al. (2020) observed that diabetic subjects displayed reduced levels of fasting glucose, insulin, high-sensitive C-reactive protein after consuming 80 mg nano-curcumin-micelle/d for 12 weeks. In the same way, a study using the same daily dose of nano-curcumin-micelle for 8 weeks was associated with glycated hemoglobin and fast blood sugar (Asadi et al., 2019). Another relevant outcome from this experiment was the reduction in the neuropathy associated with diabetes after the trial period.

Table 3
Effect of turmeric extract and curcumin in subjects at risk of diabetes and diabetic subjects.

Subjects characteristics	Experimental conditions	Study characteristics	Effect	Ref
F, 18–40 y, 60 polycystic ovarian syndrome subjects	500 mg curcumin/day for 12 weeks	R, Pc, and Db	↑ Insulin sensitivity, HDL, PPAR-γ, and LDLR expression ↓ Weight, fasting glucose, serum insulin, and dyslipidemia	(Jamilian et al., 2020)
F, 18–40 y, 60 polycystic ovarian syndrome subjects	500 mg curcumin/day for 6 weeks	R, Pc, and Db	↓ Insulin levels	(Sohaei et al., 2019)
F, 18-52y, 72 polycystic ovarian syndrome subjects	1500 mg curcumin/day for 12 weeks	R, Pc, and Db	↑ PGC1α and Gpx enzyme expression	(Heshmati et al., 2020)
F and M, 18–80 y, 60 diabetic subjects	80 mg nano-curcumin-micelle/d for 12 weeks	R, Pc, and Db	↓ Fasting glucose, insulin, high-sensitive C-reactive protein	(Shafabakhsh et al., 2020)
F and M, 30–60 y, 80 type 2 diabetic subjects	80 mg curcuminoids/d for 8 weeks	R, Pc, and Db	↓ Glycated hemoglobin, fast blood sugar, and neuropathy total score	(Asadi et al., 2019)
F and M, 40–70 y, 53 type 2 diabetic subjects	1320 mg curcuminoids/day for 10 weeks	R, Pc, and Db	↓ Fasting blood sugar level and waist circumference	(Hodaei et al., 2019)
F and M, average age: 56–60 y, 70 type-2 diabetic subjects	80 mg nano-curcumin-micelle/d for 3 months	R, Pc, and Db	↓ HbA1C, fasting blood glucose, total triglyceride, and body mass index	(Rahimi et al., 2016)
F and M, 20–85 y, 33 impaired glucose tolerance or type 2 diabetic subjects	180 mg turmeric extract/d for 6 months	R, Pc, and Db	↓ Rise of oxidized LDL	(Funamoto et al., 2019)

Subject characteristics: Female/Male, age, number of subjects; Experimental conditions: dose and experimental period; Study characteristics: R: randomized, Pc: Placebo controlled, and Dd: Double-blind; Gpx: Glutathione peroxidase; HbA1C: Glucose hemoglobin; HDL: High density lipoproteins; LDL: Low density lipoproteins; LDLR: Low-density lipoprotein receptor; PGC1α: Peroxisome proliferator activated receptor γ coactivator 1α; and PPAR-γ: Peroxisome proliferator-activated receptor gamma.

In the same line of thought, a related experiment with type 2 diabetic subjects indicated a significant reduction in fasting blood sugar level and waist circumference (Hodaei, Adibian, Nikpayam, Hedayati, & Sohrab, 2019). However, the authors did not indicate any difference in terms of insulin resistance or pancreatic B cell function between supplemented and placebo groups. The experiment carried out by Rahimi et al. (2016) indicated a similar outcome. Diabetic individual in the curcumin supplemented group displayed significant reductions in the glucose hemoglobin (HbA1C), fasting blood glucose, total triglyceride, and body mass index after consuming the 80 mg nano-curcumin-micelle/d for 3 months. In line with physiological response in terms of increasing antioxidant defense, a trial performed with type 2 diabetic and impaired glucose tolerance subjects indicated a significant reduction in the rise of oxidized LDL after 6 months of daily consumption of 180 mg turmeric extract (Funamoto et al., 2019).

4.3. Metabolic syndrome

The medical condition known as metabolic syndrome consist in the combination of different symptoms that include insulin resistance, high blood pressure, dyslipidemia, and abdominal fat deposition. The risk factors associated with this syndrome involve the overnutrition (especially carbohydrates), sedentarism, increased waist circumference, high LDL as well as low HDL levels, elevated fasting glycemia, and insulin resistance (Carnethon et al., 2004; Rizzo et al., 2013; Saklayen, 2018).

The main consequence of the evolution of metabolic syndrome are the occurrence of cardiovascular diseases. This condition require a management strategy that takes into account each component of metabolic syndrome (Grundy, Hansen, Smith, Cleeman, & Kahn, 2004). The role of curcuminoids in the context of metabolic syndrome may be explained by the modulation of key molecules and pathways related to metabolic syndrome: glucose and fat metabolism, oxidative stress and inflammatory process (Kelany, Hakami, & Omar, 2017). For instance, inhibiting the synthesis of tumor necrosis factor-α, reducing the serum levels of aspartate aminotransferase and alanine aminotransferase as well as inducing catalase activity and reducing the oxidative stress were indicated as key effects in recent studies (Bulboacă, Bolboacă, & Suciu, 2016; Kelany et al., 2017).

Table 4 displays the outcomes of clinical trials with turmeric extract and curcumin in subjects at risk of metabolic syndrome and diagnosed subjects. For instance, Yang et al. (2014) reported that the daily consumption of 1890 mg curcumin for 12 weeks by subjects with metabolic syndrome significantly decreased the levels of LDL and total triglycerides as well as increased HDL level. However, the authors did not report a significant effect weight or glucose level.

Another relevant aspect related to this disease is the oxidative stress derived from obesity in metabolic syndrome (Furukawa et al., 2004). In this sense, Safarian et al. (2019) explored the effect of curcumin (200 mg/d in free or phospholipidated form) intake in levels of Zn and Cu of metabolic syndrome subjects. The authors observed that curcumin in free form was the more efficient to increase the levels of Zn than phospholipidated one. However, no significant effect was reported for Cu regardless of curcumin form after 6 weeks of trial.

In another strategy to improve the cardiovascular status of metabolic syndrome subjects, Panahi et al. (2016) reported an improvement in adiponectin and leptin levels. While an increase in adiponectin (associated with a cardioprotective effect) level was observed in supplemented arm of the trial, a reduction in leptin (related to increased adiposity and insulin resistance) level was also reported in this group of subjects. A related experiment carried out by Osali (2020) indicated significant changes in the levels of IL and brain derived neurotrophic factor (BDNF) levels due to ingestion of curcumin associated with regular exercise. The supplemented group displayed higher levels of IL-10 and BDNF levels (reduced in metabolic syndrome subjects) and reduced IL-6 levels (increased by metabolic syndrome) in subjects of this syndrome.

The influence of curcumin ingestion (760 mg curcumin/day for 60 days) associated with a heathy diet in anthropometric measurements was evaluated by Di Pierro et al. (2015). In this experiment, the authors observed that this combination caused a significant reduction in weight loss, body fat, and waistline of metabolic syndrome subjects. A related experiment associated an improvement in the morphological characteristics of the liver with the regular consumption of 400 mg curcumin for 12 months (Selmanovic et al., 2017).

4.4. Arthritis

The disease known as arthritis is defined as the solo or simultaneous occurrence of inflammation and swelling of joints and nearby regions. Its occurrence is normally associated with pain and stiffness as well as specific symptoms. For instance, osteoarthritis is the most common type and presents degenerate effect in joints of knees, hips and hands; and rheumatoid arthritis (an autoimmune disease with lower incidence than osteoarthritis) that reduces the capacity to maintain balance and deformity in knees, wrists, and hands. The management of osteoarthritis can be carried out by using multiple approaches that include education about the disease, medication to slow the progression of the disease, rest, exercise, physical therapy and surgical correction of affected joints (Centre for Disease Control and Prevention, 2019).

The modulation of key molecules associated with arthritis is centered in the anti-inflammatory activity of curcuminoids. In this sense, previous researches indicated that curcumin reduced the levels of kinases (p38 and c-Jun N-terminal kinase and extracellular signal-regulated kinases 1 and 2) as well as the expression of nuclear factor of

Table 4
Effect of turmeric extract and curcumin in subjects at risk of metabolic syndrome and diagnosed subjects.

Subjects characteristics	Experimental conditions	Study characteristics	Effect	Ref
F and M, 65 diagnosed subjects	1890 mg curcumin/d for 12 weeks	R, Pc, and Db	↑ HDL ↓ LDL and total triglycerides	(Yang et al., 2014)
F and M, 18–65 y, 120 diagnosed subjects	200 mg curcumin/d in free or phospholipidated form for 6 weeks	R, Pc, and Db	↑ Zn, especially using phospholipidated form	(Safarian et al., 2019)
F and M, around 44 y, 100 diagnosed subjects	1000 mg curcumin/d for 8 weeks	R, Pc, and Db	↑ adiponectin level ↓ leptin level	(Panahi et al., 2016)
F, 60–65 y, 44 diagnosed subjects	9.6 mg curcuminoids/d for 6 weeks	R, Pc, and Db	↑ IL-10 and BDNF, antioxidant status ↓ IL-6	(Osali, 2020)
F and M, 18–70 y, 44 diagnosed subjects	760 mg curcumin/day for 60 days	R and Pc	Assisted in the reduction of weight loss, body fat, and waistline	(Di Pierro et al., 2015)
F and M, 35–70 y, 100 diagnosed subjects	400 mg curcumin/d for 12 months	R and Pc	Improved liver morphological characteristics	(Selmanovic et al., 2017)

Subject characteristics: Female/Male, age, number of subjects; Experimental conditions: dose and experimental period; Study characteristics: R: randomized, Pc: Placebo controlled, and Dd: Double-blind; BDNF: brain derived neurotrophic factor; HDL: High density lipoproteins; hs-CRP: high-sensitive C-reactive protein levels; IL-6 and −10: Interleukin-6 and −10; an LDL: Low density lipoproteins.

activated T cells, c-Fos, and receptor activator of nuclear factor κB (Shang et al., 2016). The anti-inflammatory activity of curcumin was also reported in terms of inhibited neutrophil activation, synoviocyte proliferation and angiogenesis, especially in the inhibition of collagenase and stromelysin expression (Jackson, Higo, Hunter, & Burt, 2006). Additionally, curcumin can also induce anti-inflammatory effect by reducing the levels of tumor necrosis factor-α and IL-17 (Wang et al., 2019).

Curcuminoids can assist in the management of arthritis by improving the status of patients and reducing the perception of pain, number of swollen and tender joints, and also inducing the anti-inflammatory response (Table 5). Regarding the influence of curcumin in the management of osteoarthritis, the recent study performed by Nakagawa et al. (2014) indicated a significant improvement in the perception of knee pain after the consumption of 180 mg curcumin/d for 8 weeks. Moreover, the authors also indicated that the number of patients requiring additional medication for pain was significantly reduced in the group consuming the supplement. In a similar way, Panahi et al. (2014) obtained higher scores in the physical function score carried out with patients in the curcumin supplemented group (1500 mg curcumin/d for 6 weeks) than in placebo one. Moreover, the patients that consumed curcumin showed lower scores in the Western Ontario and McMaster Universities osteoarthritis index (WOMAC), visual analogue scale (VAS), Lequesne's pain functional index (LPFI) tests.

Regarding the effect of curcumin in rheumatoid arthritis, this natural polyphenol was associated with improved score in ACR20 test after the daily consumption of 250 or 500 mg during 90 days (Amalraj et al., 2017). Additionally, the authors also observed that lower scores in DAS28 and VAS as well as lower levels of ESR, CRP, and rheumatoid factor (RF) and reduced number of swollen and tender joints in comparison to the other patients taking the placebo supplement. A similar experiment was carried out by Jacob et al. (2019) who tested lower daily intakes of curcumin supplement (63.32 or 126.65 mg curcuminoids) for 3 months in subjects with rheumatoid arthritis. Collectively, these studies indicate a positive association between the intake of curcumin and the management of arthritis, which indicate an analgesic and anti-inflammatory effect.

4.5. Mental health and disorders

The importance of mental health and adequate care of population with mental disorders has been increasing recently. The concern around this topic is largely due to the increasing number of cases of mental conditions that impair normal activities, learning, and work perform in global population. Depression is the most common cause of disability while suicide ranks high among main causes of death associated with mental health (World Health Organization. (2020) (2020), 2020). Preventive interventions to avoid the development and management of mental disorders includes the combination of multiple strategies: avoiding risk factors, increasing protective actions, and balancing key metabolites and mechanisms (Arango et al., 2018).

Curcuminoids fits in this context by improving the mental status, modulating key molecules, and assisting in the management of disorders. The mechanisms that explain the biological effect of curcuminoids in the context of mental disorders seems to involve different pathways. In the case of depression some relevant mechanisms are the inhibition of monoamine oxidase release, the modulation of serotonin and dopamine production as well as the neurotrophic factors and kynurenine pathways, and the amelioration of neuroinflammation (Li et al., 2020; Liu et al., 2014; Saied, Georgy, Hussien, & Hassan, 2020; Zhang et al., 2019). Particularly for schizophrenia, a recent study indicated that curcumin improved oxidative status and mitochondrial function by modulating mitochondrial complex II activity, membrane potential, and ATP level (Naserzadeh et al., 2018).

Regarding the influence on healthy subjects, many authors obtained meaningful mental improvements with the regular consumption of turmeric extract or curcumin (Table 6). For instance, Cox, White, Pipingas, Poorun, and Scholey (2020) observed that the supplemented group (80 mg curcumin/d for 12 weeks) displayed higher working memory performance than subjects in the placebo group. Moreover, the consumption of curcumin reduced the anger, confusion, fatigue, tension, and total mood disturbance. A related study obtained improvements in the verbal, visual memory, and attention in the group of subjects consuming 180 mg curcumin/d for 18 months (Small et al., 2018). This study also indicated that curcumin reduced the binding of tau protein (a metabolite associated with dementia) in amygdala and hypothalamus.

In the same line of thought, DiSilvestro et al. (2012) obtained significant reduction of plasma beta amyloid protein after the daily consumption of 80 mg curcumin for 4 weeks in healthy subjects. Another relevant outcome related to the benefits of curcuminoid consumption for mental health was reported Rainey-Smith et al. (2016). According to the authors, a significant reduction in the Montreal Cognitive Assessment test (MCA) were obtained after the intervention with turmeric extract. However, no effect was reported for cognitive function and mood between placebo and treatment groups.

In the case of depression, different studies indicate significant improvements in the status of subjects. For instance, Lopresti, Maes, Maker, Hood, and Drummond (2014) obtained significant interaction between treatment and time for IDS-SR_{30} test. According to authors, the daily consumption of 880 mg curcuminoids reduced total and mood scores after 4 and 8 weeks of trial in comparison to placebo group. Similarly, Kanchanatawan et al. (2018) observed significant differences between placebo and supplemented group in the Montgomery-Asberg Depression Rating Scale (MADRS) after 12 weeks, especially for male subjects. Moreover, the authors also indicated that the reduction in the MADRS persisted after 16 weeks (4 weeks after the end of trial).

Table 5
Effect of turmeric extract and curcumin in diagnosed with osteoarthritis and rheumatoid arthritis.

Subjects characteristics	Experimental conditions	Study characteristics	Effect	Ref
F and M, >40 y, 50 subjects with osteoarthritis	180 mg curcumin/d for 8 weeks	R, and Pc	↓ Knee pain and dependence on celecoxib	(Nakagawa et al., 2014)
F and M, around 59 y, 40 subjects with knee osteoarthritis	1500 mg curcumin/d for 6 weeks	R, Pc and Db	↑ Physical function score ↓ WOMAC, VAS, LPFI scores	(Panahi et al., 2014)
F and M, 22–55 y, 60 subjects with rheumatoid arthritis	250 or 500 mg curcumin/d for 90 days	R, Pc, and Db	↑ ACR20 test ↓ DAS28, VAS, ESR, CRP, RF, number of swollen and tender joints	(Amalraj et al., 2017)
F and M, 18–65 y, 24 subjects with rheumatoid arthritis	63.32 or 126.65 mg curcuminoids/d for 3 months	R, Pc, and Db	↑ ACR test ↓ DAS28, VAS, ESR, CRP, RF, number of swollen and tender joints	(Jacob et al., 2019)

Subject characteristics: Female/Male, age, number of subjects; Experimental conditions: dose and experimental period; Study characteristics: R: randomized, Pc: Placebo controlled, and Dd: Double-blind; ACR20: American College of Rheumatology 20%; CRP: C-Reactive protein; DAS28: Disease Activity Score-28; ESR: Erythrocyte Sedimentation Rate; LPFI: Lequesne's pain functional index; RF: Rheumatoid Factor; VAS: Visual Analogue Scale (VAS); and WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index.

Table 6
Effect of turmeric extract and curcumin in mental health and disorders.

Subjects characteristics	Experimental conditions	Study characteristics	Effect	Ref
F and M, 50–85 y, 79 healthy subjects	80 mg curcumin/d for 12 weeks	R, PC, and Db	↑ Working memory performance ↓ Fatigue, tension, anger, confusion and total mood disturbance	(Cox et al., 2020)
F and M, 51–84 y, 40 healthy subjects	180 mg curcumin/d for 18 months	R, Pc, and Db	↑ Verbal, visual memory, and attention ↓ Binding of tau protein in amygdala and hypothalamus	(Small et al., 2018)
F and M, 40–60 y, 38 healthy subjects	80 mg curcumin/d for 4 weeks	R and Pc	↓ Plasma beta amyloid protein	(DiSilvestro et al., 2012)
F and M, 40–90 y, 96 healthy subjects	1320 mg curcuminoids/d for 12 months	R, Pc, and Db	↓ MCA score	(Rainey-Smith et al., 2016)
F and M, 18–65 y, 56 subjects with major depression	880 mg curcuminoids/d for 8 weeks	R, Pc, and Db	↓ IDS-SR$_{30}$ total and mood score	(Lopresti et al., 2014)
F and M, 18–63 y, 65 subjects with major depression	From 500 to 1500 mg curcuminoids/d for 4 weeks followed by 1500 mg curcuminoids/d for 8 weeks	R, Pc, and Db	↓ MADRS score	(Kanchanatawan et al., 2018)
F and M, 18–65 y, 123 subjects with major depression	500 and 1000 mg curcumin/d and 500 mg curcumin + 30 g saffron/d for 12 weeks	R, Pc, and Db	↓ Depression and anxiety	(Lopresti & Drummond, 2017)
F and M, 18–65 y, 50 subjects with major depression	880 mg curcuminoids/d for 8 weeks	R, Pc, and Db	↑ Urinary thromboxane B2, substance P and cortisol levels	(Lopresti et al., 2015)
F and M, 18–65 y, 38 subjects with chronic schizophrenia	3000 mg curcumin/d with antipsychotics for over 2 years	R, Pc, and Db	↓ Total PANSS and negative symptoms score	(Miodownik et al., 2019)
F and M, 5–51 y, 12 subjects with chronic schizophrenia	180 mg curcumin/d with antipsychotics for 8 weeks	R, Pc, and Db	↑ Working memory ↓ IL-6 level	(Kucukgoncu et al., 2019)

Subject characteristics: Female/Male, age, number of subjects; Experimental conditions: dose and experimental period; Study characteristics: R: randomized, Pc: Placebo controlled, and Dd: Double-blind; CDSS: Calgary Depression Scale for Schizophrenia; IDS-SR$_{30}$: Inventory of Depressive Symptomatology self-rated version; IL-6: Interleukin 6; MADRS: Montgomery-Asberg Depression Rating Scale; MCA: Montreal Cognitive Assessment; and PANSS: Positive and Negative Symptoms Scale.

Likewise, the experiment carried out with chronically depressed subjects by Lopresti and Drummond (2017) indicated reductions in the depressive symptoms and anxiety after the consumption of curcumin alone or combined with saffron. In another experiment of the same research group, significant differences were obtained in the concentration of urinary thromboxane B2, substance P and plasma cortisol levels (Lopresti et al., 2015). Additionally, the authors also observed that the reduction in IDS-SR$_{30}$ score by consuming curcumin were greater in those individuals that displayed higher baseline levels of endothelin-1 peptide.

Another important mental disorder that may be better managed with curcumin supplementation is chronic schizophrenia. The study carried out by Miodownik et al. (2019) indicated that the consumption of 3000 mg curcumin/d lead to lower scores in Positive and Negative Symptoms Scale (PNSS) test after 6 months in subjects with chronic schizophrenia. In a related experiment with patients with the same disease, Kucukgoncu, Guloksuz, and Tek (2019) observed that the curcumin supplementation improve the working memory and also reduce the levels of IL-6.

5. Development of function food products with turmeric

The production of functional foods using curcuminoids faces important challenges that must be tackle in order to offer adequate products to consumers. Important factors that must be considered are: bioaccessibility and processing conditions. In terms of bioaccessibility, the main concern is the related to poor solubility of curcuminoids in water that limits their solubility in the intestinal tract and eventually reduce their absorption (Cas & Ghidoni, 2019). In this sense, the production of emulsified systems that facilitates the dispersion of curcuminoids in an aqueous medium can bring important benefits to explore the biological activity of curcuminoids. For instance, Zhang et al. (2016) developed polysaccharide-based hydrogel beads loaded with curcumin and obtained a better control and release of encapsulated active component. In the same line of thought, Zheng, Peng, Zhang, and McClements (2018) compared the bioaccessibility of three emulsification methods (oil-loading, heating, and pH change methods) with commercial turmeric extracts. According to the authors, the method with pH modification and the commercial product CurcuWin® (OmniActive) displayed the highest bioaccessibility indexes in comparison to other methods and commercial products.

In relation to commercial products, it is relevant to mention that some options are available in the market. CurcuWin® (OmniActive), LongVida® (Ingennus), NovaSol® (CleanFoods), and Theracurmin® (Natural Factors) can be cited as turmeric extracts with improved bioaccessibility (Jamwal, 2018). It is also relevant to mention that the some of the studies included in this review were carried out using turmeric extracts and curcumin supplements that were improved to have better bioaccessibility, such as (Campbell & Ouyang, 2019; Cox et al., 2020; Di Pierro et al., 2015; DiSilvestro et al., 2012; Panahi et al., 2014; Rahimi et al., 2016). This outcome supports the role of turmeric extract and curcuminoids as functional ingredients.

To the best of our knowledge, only a single study explored the healthy benefits of curcumin in a functional food (Ferguson et al., 2019). In his case, the authors evaluated the effect of curcumin in combination with phytosterols in bread in the plasma lipid profile of subjects with hypercholesterolemia (randomized, placebo-controlled, double blind). No significant effect was observed in relation to curcumin addition in bread whereas the incorporation of phytosterols induced a reduction in the levels of plasma cholesterol. Additionally, the authors indicated that this lack of effect observed for curcumin could be explained by the high temperatures used to process bread, which favored the degradation of curcumin.

It is also worth mentioning that the incorporation of turmeric extract in beverages, bread, biscuits, snacks, pasta, milk, cheese, fresh sausage, and patties has been studied (Adegoke, Oyekunle, & Afolabi, 2017; Al-Obaidi, 2019; de Carvalho et al., 2020; Gómez-Estaca, Pintado, Jiménez-Colmenero, & Cofrades, 2020; Hefnawy, El-Shourbagy, & Ramadan, 2016; Lodh, Khamrui, & Prasad, 2018; Oliveira et al., 2020; Park et al., 2019; Wahanik, Neri-Numa, Pastore, Chang, & Clerici, 2018; Zanzer et al., 2017) (Fig. 2). In general, this natural and functional ingredient produces minimal impact in the physic-chemical properties, improves antioxidant capacity, delays microbial growth but can influence the color and sensory properties.

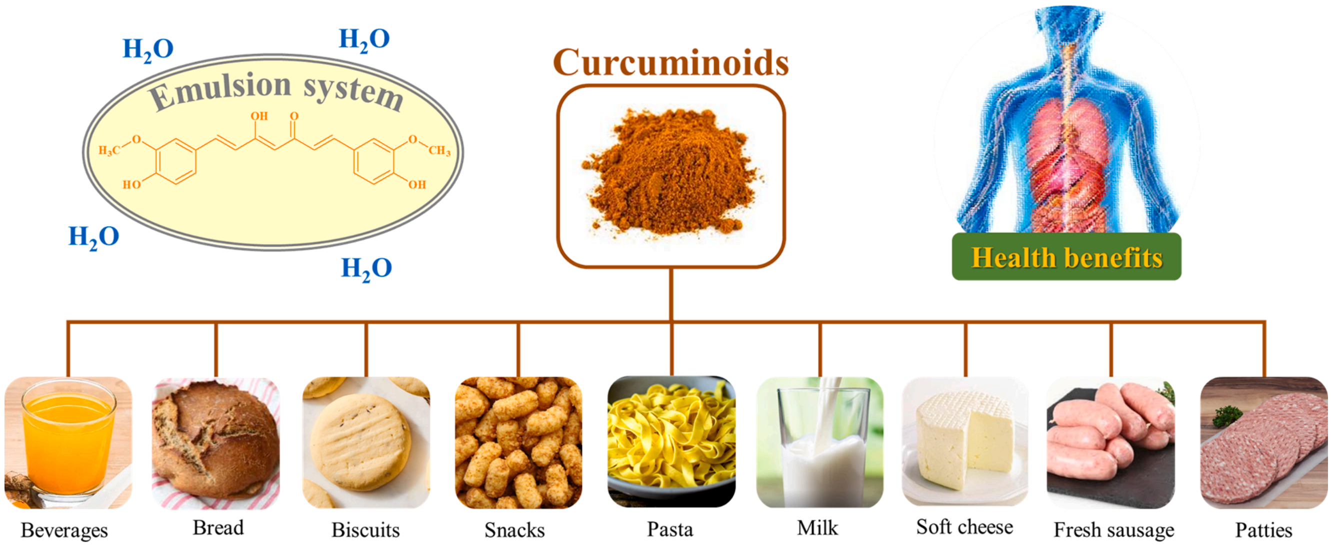

Fig. 2. Functional foods enrich with curcuminoids in recent studies.

6. Conclusion

The curcuminoids present in turmeric have great potential as functional ingredients. Once the demand for curcuminoids increase, environmentally friendly systems will receive even more attention. US, MW, pressurized hot water and SC-CO_2 extract are the main options. Curcumin (as the main compound of this category) has been associated with important physiological effects to assist in the reduction of risk associated with some of main diseases that affect global population as well as in the management of these diseases. The challenge imposed by the poor bioaccessibility can be overcame by the development of emulsions that preserve the biological activity of curcuminoids. However, major advances are still necessary, particularly in terms of functional foods development. More information about the effect of food processing and storage conditions in the biological activity of curcuminoids is necessary. Defining adequate concentration of curcuminoids, emulsifying agents, processing and storage conditions can be seen as next challenges for researchers studying these bioactive compounds in foods with conventional and healthier formulations.

7. Ethics statement

Our research did not include any human subjects and animal experiments.

Declaration of Competing Interest

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

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References

Adegoke, G. O., Oyekunle, A. O., & Afolabi, M. O. (2017). Functional biscuits from wheat, soya bean and turmeric (*Curcuma longa*): Optimization of ingredients levels using response surface methodology. *Research Journal of Food and Nutrition, 1*(1), 13–22. https://doi.org/10.1007/s00217-003-0683-6.

Akazawa, N., Choi, Y., Miyaki, A., Tanabe, Y., Sugawara, J., Ajisaka, R., & Maeda, S. (2013). Effects of curcumin intake and aerobic exercise training on arterial compliance in postmenopausal women. *Artery Research, 7*(1), 67–72. https://doi.org/10.1016/j.artres.2012.09.003.

Al-Obaidi, L. F. H. (2019). Effect of adding different concentrations of turmeric powder on the chemical composition, oxidative stability and microbiology of the soft cheese. *Plant Archives, 19*(2), 317–321.

Amalraj, A., Varma, K., Jacob, J., Divya, C., Kunnumakkara, A. B., Stohs, S. J., & Gopi, S. (2017). A novel highly bioavailable curcumin formulation improves symptoms and diagnostic indicators in rheumatoid arthritis patients: A randomized, double-blind, placebo-controlled, two-dose, three-arm, and parallel-group study. *Journal of Medicinal Food, 20*(10), 1022–1030. https://doi.org/10.1089/jmf.2017.3930.

Ameer, K., Shahbaz, H. M., & Kwon, J.-H. (2017). Green extraction methods for polyphenols from plant matrices and their byproducts: A review. *Comprehensive Reviews in Food Science and Food Safety, 16*(2), 295–315. https://doi.org/10.1111/1541-4337.12253.

American Diabetes Association. (2014). Diagnosis and classification of diabetes mellitus. *Diabetes Care, 37*(S1), S81–S90. https://doi.org/10.2337/dc14-S081.

American Diabetes Association. (2019). 2. Classification and diagnosis of diabetes: Standards of medical care in diabetes-2019. *Diabetes Care, 42*(Supplement 1), S13–S28. https://doi.org/10.2337/dc19-S002.

Arango, C., Díaz-Caneja, C. M., McGorry, P. D., Rapoport, J., Sommer, I. E., Vorstman, J. A., … Carpenter, W. (2018). Preventive strategies for mental health. *The Lancet Psychiatry, 5*(7), 591–604. https://doi.org/10.1016/S2215-0366(18)30057-9.

Asadi, S., Gholami, M. S., Siassi, F., Qorbani, M., Khamoshian, K., & Sotoudeh, G. (2019). Nano curcumin supplementation reduced the severity of diabetic sensorimotor polyneuropathy in patients with type 2 diabetes mellitus: A randomized double-blind placebo- controlled clinical trial. *Complementary Therapies in Medicine, 43*, 253–260. https://doi.org/10.1016/j.ctim.2019.02.014.

Barber-Chamoux, N., Milenkovic, D., Verny, M. A., Habauzit, V., Pereira, B., Lambert, C., … Morand, C. (2018). Substantial variability across individuals in the vascular and nutrigenomic response to an acute intake of curcumin: A randomized controlled trial. *Molecular Nutrition and Food Research, 62*(5), 1700418. https://doi.org/10.1002/mnfr.201700418.

Bulboacă, A., Bolboacă, S. D., & Suciu, H. S. (2016). Protective effect of curcumin in fructose-induced metabolic syndrome and in streptozotocin-induced diabetes in rats. *Iranian Journal of Basic Medical Sciences, 19*(6), 585–593. https://doi.org/10.22038/ijbms.2016.7125.

Campbell, M. S., & Fleenor, B. S. (2018). The emerging role of curcumin for improving vascular dysfunction: A review. *Critical Reviews in Food Science and Nutrition, 58*(16), 2790–2799. https://doi.org/10.1080/10408398.2017.1341865.

Campbell, M. S., Ouyang, A., I.M., K., Charnigo, R. J., Westgate, P. M., & Fleenor, B. S. (2019). Influence of enhanced bioavailable curcumin on obesity-associated cardiovascular disease risk factors and arterial function: A double-blinded, randomized, controlled trial. Nutrition, 62, 135–139. https://doi.org/10.1016/j.nut.2019.01.002.

Carnethon, M. R., Loria, C. M., Hill, J. O., Sidney, S., Savage, P. J., & Liu, K. (2004). Risk factors for metabolic syndrome: The Coronary Artery Risk Development in Young Adults (CARDIA) study, 1985–2001. *Diabetes Care, 27*(11), 2707–2715. https://doi.org/10.2337/diacare.27.11.2707.

Cas, M. D., & Ghidoni, R. (2019). Dietary curcumin: Correlation between bioavailability and health potential. *Nutrients, 11*(9), 2147. https://doi.org/10.3390/nu11092147.

Centers for Disease Control & Prevention. (2020). Prediabetes - Your chance to prevent type 2 diabetes. Retrieved from https://www.cdc.gov/diabetes/basics/prediabetes.html.

Centre for Disease Control and Prevention. (2019). Arthritis types. Retrieved from https://www.cdc.gov/arthritis/basics/types.html.

Chemat, F., Abert Vian, M., Fabiano-Tixier, A.-S. S., Nutrizio, M., Režek Jambrak, A., Munekata, P. E. S., … Cravotto, G. (2020). A review of sustainable and intensified techniques for extraction of food and natural products. *Green Chemistry, 22*(8), 2325–2353. https://doi.org/10.1039/c9gc03878g.

Coban, D., Milenkovic, D., Chanet, A., Khallou-Laschet, J., Sabbe, L., Palagani, A., … Morand, C. (2012). Dietary curcumin inhibits atherosclerosis by affecting the expression of genes involved in leukocyte adhesion and transendothelial migration. *Molecular Nutrition and Food Research, 56*(8), 1270–1281. https://doi.org/10.1002/mnfr.201100818.

Correa, F., Buelna-Chontal, M., Hernández-Reséndiz, S., García-Niño, W. R., Roldán, F. J., Soto, V., … Zazueta, C. (2013). Curcumin maintains cardiac and mitochondrial function in chronic kidney disease. *Free Radical Biology and Medicine, 61*, 119–129. https://doi.org/10.1016/j.freeradbiomed.2013.03.017.

Cox, K. H. M., White, D. J., Pipingas, A., Poorun, K., & Scholey, A. (2020). Further evidence of benefits to mood and working memory from lipidated curcumin in healthy older people: A 12-week, double-blind, placebo-controlled, partial replication study. *Nutrients, 12*(6), 1–20. https://doi.org/10.3390/nu12061678.

de Carvalho, F. A. L., Munekata, P. E. S., Lopes de Oliveira, A., Pateiro, M., Domínguez, R., Trindade, M. A., & Lorenzo, J. M. (2020). Turmeric (*Curcuma longa* L.) extract on oxidative stability, physicochemical and sensory properties of fresh lamb sausage with fat replacement by tiger nut (*Cyperus esculentus* L.) oil. *Food Research International, 136*, Article 109487. https://doi.org/10.1016/j.foodres.2020.109487.

Di Pierro, F., Bressan, A., Ranaldi, D., Rapacioli, G., Giacomelli, L., & Bertuccioli, A. (2015). Potential role of bioavailable curcumin in weight loss and omental adipose tissue decrease: Preliminary data of a randomized, controlled trial in overweight people with metabolic syndrome. Preliminary study. *European Review for Medical and Pharmacological Sciences, 19*(21), 4195–4202.

DiSilvestro, R. A., Joseph, E., Zhao, S., & Bomser, J. (2012). Diverse effects of a low dose supplement of lipidated curcumin in healthy middle aged people. *Nutrition Journal, 11*(1), 1–8. https://doi.org/10.1186/1475-2891-11-79.

El-Moselhy, M. A., Taye, A., Sharkawi, S. S., El-Sisi, S. F. I., & Ahmed, A. F. (2011). The antihyperglycemic effect of curcumin in high fat diet fed rats. Role of TNF-α and free fatty acids. *Food and Chemical Toxicology, 49*(5), 1129–1140. https://doi.org/10.1016/j.fct.2011.02.004.

Euterpio, M. A., Cavaliere, C., Capriotti, A. L., & Crescenzi, C. (2011). Extending the applicability of pressurized hot water extraction to compounds exhibiting limited water solubility by pH control: Curcumin from the turmeric rhizome. *Analytical and Bioanalytical Chemistry, 401*(9), 2977–2985. https://doi.org/10.1007/s00216-011-5383-7.

Ferguson, J. J. A., Wolska, A., Remaley, A. T., Stojanovski, E., MacDonald-Wicks, L., & Garg, M. L. (2019). Bread enriched with phytosterols with or without curcumin modulates lipoprotein profiles in hypercholesterolaemic individuals. A randomised controlled trial. *Food and Function, 10*(5), 2515–2527. https://doi.org/10.1039/c8fo02512f.

Funamoto, M., Shimizu, K., Sunagawa, Y., Katanasaka, Y., Miyazaki, Y., Kakeya, H., … Morimoto, T. (2019). Effects of highly absorbable curcumin in patients with impaired glucose tolerance and non-insulin-dependent diabetes mellitus. *Journal of Diabetes Research, 2019*. https://doi.org/10.1155/2019/8208237.

Furukawa, S., Fujita, T., Shimabukuro, M., Iwaki, M., Yamada, Y., Nakajima, Y., … Shimomura, I. (2004). Increased oxidative stress in obesity and its impact on metabolic syndrome. *Journal of Clinical Investigation, 114*(12), 1752–1761. https://doi.org/10.1172/JCI21625.

Gómez-Estaca, J., Pintado, T., Jiménez-Colmenero, F., & Cofrades, S. (2020). The effect of household storage and cooking practices on quality attributes of pork burgers formulated with PUFA- and curcumin-loaded oleogels as healthy fat substitutes. *Lwt, 119*, Article 108909. https://doi.org/10.1016/j.lwt.2019.108909.

Gonzales, A. M., & Orlando, R. A. (2008). Curcumin and resveratrol inhibit nuclear factor-kappaB-mediated cytokine expression in adipocytes. *Nutrition and Metabolism, 5*(1), 1–13. https://doi.org/10.1186/1743-7075-5-17.

Granato, D., Barba, F. J., Bursać Kovačević, D., Lorenzo, J. M., Cruz, A. G., & Putnik, P. (2020). Functional foods: Product development, technological trends, efficacy testing, and safety. *Annual Review of Food Science and Technology, 11*(1), 93–118. https://doi.org/10.1146/annurev-food-032519-051708.

Grundy, S. M., Hansen, B., Smith, S. C., Cleeman, J. I., & Kahn, R. A. (2004). Clinical management of metabolic syndrome: Report of the American Heart Association/National Heart, Lung, and Blood Institute/American Diabetes Association Conference on scientific Issues related to management. *Circulation, 109*(4), 551–556. https://doi.org/10.1161/01.CIR.0000112379.88385.67.

Gutierres, V. O., Assis, R. P., Arcaro, C. A., Oliveira, J. O., Lima, T. F. O., Beretta, A. L. R. Z., … Brunetti, I. L. (2019). Curcumin improves the effect of a reduced insulin dose on glycemic control and oxidative stress in streptozotocin-diabetic rats. *Phytotherapy Research, 33*(4), 976–988. https://doi.org/10.1002/ptr.6291.

He, H., Luo, Y., Qiao, Y., Zhang, Z., Yin, D., Yao, J., … He, M. (2018). Curcumin attenuates doxorubicin-induced cardiotoxicity via suppressing oxidative stress and preventing mitochondrial dysfunction mediated by 14–3-3γ. *Food and Function, 9*(8), 4404–4418. https://doi.org/10.1039/c8fo00466h.

Hefnawy, H. T., El-Shourbagy, G. A., & Ramadan, M. F. (2016). Phenolic extracts of carrot, grape leaf and turmeric powder: Antioxidant potential and application in biscuits. *Journal of Food Measurement and Characterization, 10*(3), 576–583. https://doi.org/10.1007/s11694-016-9339-7.

Heshmati, J., Golab, F., Morvaridzadeh, M., Potter, E., Akbari-Fakhrabadi, M., Farsi, F., … Shidfar, F. (2020). The effects of curcumin supplementation on oxidative stress, Sirtuin-1 and peroxisome proliferator activated receptor γ coactivator 1α gene expression in polycystic ovarian syndrome (PCOS) patients: A randomized placebo-controlled clinical trial. *Diabetes and Metabolic Syndrome: Clinical Research and Reviews, 14*(2), 77–82. https://doi.org/10.1016/j.dsx.2020.01.002.

Hirun, S., Utama-ang, N., & Roach, P. D. (2014). Turmeric (*Curcuma longa* L.) drying: An optimization approach using microwave-vacuum drying. *Journal of Food Science and Technology, 51*(9), 2127–2133. https://doi.org/10.1007/s13197-012-0709-9.

Hodaei, H., Adibian, M., Nikpayam, O., Hedayati, M., & Sohrab, G. (2019). The effect of curcumin supplementation on anthropometric indices, insulin resistance and oxidative stress in patients with type 2 diabetes: A randomized, double-blind clinical trial. *Diabetology and Metabolic Syndrome, 11*(1), 1–8. https://doi.org/10.1186/s13098-019-0437-7.

Huang, Z., Ye, B., Dai, Z., Wu, X., Lu, Z., Shan, P., & Huang, W. (2015). Curcumin inhibits autophagy and apoptosis in hypoxia/reoxygenation-induced myocytes. *Molecular Medicine Reports, 11*(6), 4678–4684. https://doi.org/10.3892/mmr.2015.3322.

Jackson, J. K., Higo, T., Hunter, W. L., & Burt, H. M. (2006). The antioxidants curcumin and quercetin inhibit inflammatory processes associated with arthritis. *Inflammation Research, 55*(4), 168–175. https://doi.org/10.1007/s00011-006-0067-z.

Jacob, J., Amalraj, A., Raj, K. K. J., Divya, C., Kunnumakkara, A. B., & Gopi, S. (2019). A novel bioavailable hydrogenated curcuminoids formulation (CuroWhite^{TM}) improves symptoms and diagnostic indicators in rheumatoid arthritis patients - A randomized, double blind and placebo controlled study. *Journal of Traditional and Complementary Medicine, 9*(4), 346–352. https://doi.org/10.1016/j.jtcme.2018.06.001.

Jamilian, M., Foroozanfard, F., Kavossian, E., Aghadavod, E., Shafabakhsh, R., Hoseini, A., & Asemi, Z. (2020). Effects of curcumin on body weight, glycemic control and serum lipids in women with polycystic ovary syndrome: A randomized, double-blind, placebo-controlled trial. *Clinical Nutrition ESPEN, 36*, 128–133. https://doi.org/10.1016/j.clnesp.2020.01.005.

Jamwal, R. (2018). Bioavailable curcumin formulations: A review of pharmacokinetic studies in healthy volunteers. *Journal of Integrative Medicine, 16*(6), 367–374. https://doi.org/10.1016/j.joim.2018.07.001.

Kanchanatawan, B., Tangwongchai, S., Sughondhabhirom, A., Suppapitiporn, S., Hemrunrojn, S., Carvalho, A. F., & Maes, M. (2018). Add-on treatment with curcumin has antidepressive effects in Thai patients with major depression: Results of a randomized double-blind placebo-controlled study. *Neurotoxicity Research, 33*(3), 621–633. https://doi.org/10.1007/s12640-017-9860-4.

Kelany, M. E., Hakami, T. M., & Omar, A. H. (2017). Curcumin improves the metabolic syndrome in high-fructosediet-fed rats: Role of TNF-α, NF-κB, and oxidative stress. *Canadian Journal of Physiology and Pharmacology, 95*(2), 140–150. https://doi.org/10.1139/cjpp-2016-0152.

Kiamahalleh, M. V., Najafpour-Darzi, G., Rahimnejad, M., Moghadamnia, A. A., & Kiamahalleh, M. V. (2016). High performance curcumin subcritical water extraction from turmeric (*Curcuma longa* L.). *Journal of Chromatography B: Analytical Technologies in the Biomedical and Life Sciences, 1022*, 191–198. https://doi.org/10.1016/j.jchromb.2016.04.021.

Kim, T., Davis, J., Zhang, A. J., He, X., & Mathews, S. T. (2009). Curcumin activates AMPK and suppresses gluconeogenic gene expression in hepatoma cells. *Biochemical and Biophysical Research Communications, 388*(2), 377–382. https://doi.org/10.1016/j.bbrc.2009.08.018.

Kucukgoncu, S., Guloksuz, S., & Tek, C. (2019). Effects of curcumin on cognitive functioning and inflammatory state in schizophrenia: A double-blind, placebo-controlled pilot trial. *Journal of Clinical Psychopharmacology, 39*(2), 182–184. https://doi.org/10.1097/JCP.0000000000001012.

Kuttigounder, D., Lingamallu, J. R., & Bhattacharya, S. (2011). Turmeric powder and starch: Selected physical, physicochemical, and microstructural properties. *Journal of Food Science, 76*(9), C1284–C1291. https://doi.org/10.1111/j.1750-3841.2011.02403.x.

Li, J., Chen, L., Li, G., Chen, X., Hu, S., Zheng, L., … Yu, Y. (2020). Sub-acute treatment of curcumin derivative J147 ameliorates depression-like behavior through 5-HT1A-mediated cAMP signaling. *Frontiers in Neuroscience, 14*, 701. https://doi.org/10.3389/fnins.2020.00701.

Liu, D., Wang, Z., Gao, Z., Xie, K., Zhang, Q., Jiang, H., & Pang, Q. (2014). Effects of curcumin on learning and memory deficits, BDNF, and ERK protein expression in rats exposed to chronic unpredictable stress. *Behavioural Brain Research, 271*, 116–121. https://doi.org/10.1016/j.bbr.2014.05.068.

Lodh, J., Khamrui, K., & Prasad, W. G. (2018). Optimization of heat treatment and curcumin level for the preparation of anti-oxidant rich *ghee* from fermented buffalo cream by Central Composite Rotatable Design. *Journal of Food Science and Technology, 55*(5), 1832–1839. https://doi.org/10.1007/s13197-018-3098-x.

Lopresti, A. L., & Drummond, P. D. (2017). Efficacy of curcumin, and a saffron/curcumin combination for the treatment of major depression: A randomised, double-blind, placebo-controlled study. *Journal of Affective Disorders, 207*, 188–196. https://doi.org/10.1016/j.jad.2016.09.047.

Lopresti, A. L., Maes, M., Maker, G. L., Hood, S. D., & Drummond, P. D. (2014). Curcumin for the treatment of major depression: A randomised, double-blind, placebo controlled study. *Journal of Affective Disorders, 167*, 368–375. https://doi.org/10.1016/j.jad.2014.06.001.

Lopresti, A. L., Maes, M., Meddens, M. J. M., Maker, G. L., Arnoldussen, E., & Drummond, P. D. (2015). Curcumin and major depression: A randomised, double-blind, placebo-controlled trial investigating the potential of peripheral biomarkers to predict treatment response and antidepressant mechanisms of change. *European*

Neuropsychopharmacology, 25(1), 38–50. https://doi.org/10.1016/j.euroneuro.2014.11.015.

Maithilikarpagaselvi, N., Sridhar, M. G., Swaminathan, R. P., & Zachariah, B. (2016). Curcumin prevents inflammatory response, oxidative stress and insulin resistance in high fructose fed male Wistar rats: Potential role of serine kinases. *Chemico-Biological Interactions, 244*, 187–194. https://doi.org/10.1016/j.cbi.2015.12.012.

Meng, F.-C., Zhou, Y.-Q., Ren, D., Wang, R., Wang, C., Lin, L.-G., … Zhang, Q.-W. (2018). Turmeric: A review of its chemical composition, quality control, bioactivity, and pharmaceutical application. In *Natural and Artificial Flavoring Agents and Food Dyes* (pp. 299–350). Elsevier. https://doi.org/10.1016/b978-0-12-811518-3.00010-7.

Miodownik, C., Lerner, V., Kudkaeva, N., Lerner, P. P., Pashinian, A., Bersudsky, Y., … Bergman, J. (2019). Curcumin as add-on to antipsychotic treatment in patients with chronic schizophrenia: A randomized, double-blind, placebo-controlled study. *Clinical Neuropharmacology, 42*(4), 117–122. https://doi.org/10.1097/WNF.0000000000000344.

Mirzabeigi, P., Mohammadpour, A. H., Salarifar, M., Gholami, K., Mojtahedzadeh, M., & Javadi, M. R. (2015). The effect of curcumin on some of traditional and non-traditional cardiovascular risk factors: A pilot randomized, double-blind, placebo-controlled trial. *Iranian Journal of Pharmaceutical Research, 14*(2), 479–486. https://doi.org/10.22037/ijpr.2015.1658.

Mohammadi, A., Sahebkar, A., Iranshahi, M., Amini, M., Khojasteh, R., Ghayour-Mobarhan, M., & Ferns, G. A. (2013). Effects of supplementation with curcuminoids on dyslipidemia in obese patients: A randomized crossover trial. *Phytotherapy Research, 27*(3), 374–379. https://doi.org/10.1002/ptr.4715.

Mottahedin, P., Haghighi Asl, A., & Khajenoori, M. (2017). Extraction of curcumin and essential oil from *Curcuma longa* L. by subcritical water via response surface methodology. *Journal of Food Processing and Preservation, 41*(4), Article e13095. https://doi.org/10.1111/jfpp.13095.

Na, L. X., Zhang, Y. L., Li, Y., Liu, L. Y., Li, R., Kong, T., & Sun, C. H. (2011). Curcumin improves insulin resistance in skeletal muscle of rats. *Nutrition, Metabolism and Cardiovascular Diseases, 21*(7), 526–533. https://doi.org/10.1016/j.numecd.2009.11.009.

Nakagawa, Y., Mukai, S., Yamada, S., Matsuoka, M., Tarumi, E., Hashimoto, T., … Nakamura, T. (2014). Short-term effects of highly-bioavailable curcumin for treating knee osteoarthritis: A randomized, double-blind, placebo-controlled prospective study. *Journal of Orthopaedic Science, 19*(6), 933–939. https://doi.org/10.1007/s00776-014-0633-0.

Naserzadeh, P., Hafez, A. A., Abdorahim, M., Abdollahifar, M. A., Shabani, R., Peirovi, H., … Ashtari, K. (2018). Curcumin loading potentiates the neuroprotective efficacy of Fe_3O_4 magnetic nanoparticles in cerebellum cells of schizophrenic rats. *Biomedicine and Pharmacotherapy, 108*, 1244–1252. https://doi.org/10.1016/j.biopha.2018.09.106.

Oliveira, A. R., Ribeiro, A. E. C., Oliveira, É. R., Ribeiro, K. O., Garcia, M. C., Careli-Gondim, Í., … Caliari, M. (2020). Physicochemical, microbiological and sensory characteristics of snacks developed from broken rice grains and turmeric powder. *International Journal of Food Science and Technology, 55*(7), 2719–2729. https://doi.org/10.1111/ijfs.14525.

Oliver, J. M., Stoner, L., Rowlands, D. S., Caldwell, A. R., Sanders, E., Kreutzer, A., … Jäger, R. (2016). Novel form of curcumin improves endothelial function in young, healthy individuals: A double-blind placebo controlled study. *Journal of Nutrition and Metabolism, 2016*. https://doi.org/10.1155/2016/1089653.

Osali, A. (2020). Aerobic exercise and nano-curcumin supplementation improve inflammation in elderly females with metabolic syndrome. *Diabetology and Metabolic Syndrome, 12*(1), 26. https://doi.org/10.1186/s13098-020-00532-4.

Panahi, Y., Hosseini, M. S., Khalili, N., Naimi, E., Soflaei, S. S., Majeed, M., & Sahebkar, A. (2016). Effects of supplementation with curcumin on serum adipokine concentrations: A randomized controlled trial. *Nutrition, 32*(10), 1116–1122. https://doi.org/10.1016/j.nut.2016.03.018.

Panahi, Y., Rahimnia, A. R., Sharafi, M., Alishiri, G., Saburi, A., & Sahebkar, A. (2014). Curcuminoid treatment for knee osteoarthritis: A randomized double-blind placebo-controlled trial. *Phytotherapy Research, 28*(11), 1625–1631. https://doi.org/10.1002/ptr.5174.

Park, S. J., Hong, S. J., Garcia, C. V., Lee, S. B., Shin, G. H., & Kim, J. T. (2019). Stability evaluation of turmeric extract nanoemulsion powder after application in milk as a food model. *Journal of Food Engineering, 259*, 12–20. https://doi.org/10.1016/j.jfoodeng.2019.04.011.

Paulucci, V. P., Couto, R. O., Teixeira, C. C. C., & Freitas, L. A. P. (2013). Optimization of the extraction of curcumin from *Curcuma longa* rhizomes. *Brazilian Journal of Pharmacognosy, 23*(1), 94–100. https://doi.org/10.1590/S0102-695X2012005000117.

Peram, M. R., Jalalpure, S. S., Joshi, S. A., Palkar, M. B., & Diwan, P. V. (2017). Single robust RP-HPLC analytical method for quantification of curcuminoids in commercial turmeric products, Ayurvedic medicines, and nanovesicular systems. *Journal of Liquid Chromatography and Related Technologies, 40*(10), 487–498. https://doi.org/10.1080/10826076.2017.1329742.

Pivari, F., Mingione, A., Brasacchio, C., & Soldati, L. (2019). Curcumin and type 2 diabetes mellitus: Prevention and treatment. *Nutrients, 11*(8), 1837. https://doi.org/10.3390/nu11081837.

Priyadarsini, K. I. (2014). The chemistry of curcumin: From extraction to therapeutic agent. *Molecules, 19*(12), 20091–20112. https://doi.org/10.3390/molecules191220091.

Putnik, P., Lorenzo, J., Barba, F., Roohinejad, S., Režek Jambrak, A., Granato, D., … Bursać Kovačević, D. (2018). Novel food processing and extraction technologies of high-added value compounds from plant materials. *Foods, 7*, 106. https://doi.org/10.3390/foods7070106.

Rahimi, H. R., Mohammadpour, A. H., Dastani, M., Jaafari, M. R., Abnous, K., Ghayour Mobarhan, M., & Kazemi Oskuee, R. (2016). The effect of nano-curcumin on HbA1c, fasting blood glucose, and lipid profile in diabetic subjects: A randomized clinical trial. *Avicenna Journal of Phytomedicine, 6*(5), 567–577. https://doi.org/10.22038/ajp.2016.6761.

Rainey-Smith, S. R., Brown, B. M., Sohrabi, H. R., Shah, T., Goozee, K. G., Gupta, V. B., & Martins, R. N. (2016). Curcumin and cognition: A randomised, placebo-controlled, double-blind study of community-dwelling older adults. *British Journal of Nutrition, 115*(12), 2106–2113. https://doi.org/10.1017/S0007114516001203.

Rizzo, A. C. B., Goldberg, T. B. L., Silva, C. C., Kurokawa, C. S., Nunes, H. R. C., & Corrente, J. E. (2013). Metabolic syndrome risk factors in overweight, obese, and extremely obese Brazilian adolescents. *Nutrition Journal, 12*(1), 1–7. https://doi.org/10.1186/1475-2891-12-19.

Rouse, M., Younès, A., & Egan, J. M. (2014). Resveratrol and curcumin enhance pancreatic β-cell function by inhibiting phosphodiesterase activity. *Journal of Endocrinology, 223*(2), 107–117. https://doi.org/10.1530/JOE-14-0335.

Safarian, H., Parizadeh, S. M. R., Saberi-Karimain, M., Darroudi, S., Javandoost, A., Mohammadi, F., … Mohebati, M. (2019). The effect of curcumin on serum copper and zinc and Zn/Cu ratio in individuals with metabolic syndrome: A double-blind clinical trial. *Journal of Dietary Supplements, 16*(6), 625–634. https://doi.org/10.1080/19390211.2018.1472711.

Sahne, F., Mohammadi, M., Najafpour, G. D., & Moghadamnia, A. A. (2016). Extraction of bioactive compound curcumin from turmeric (Curcuma longa L.) via different routes: A comparative study. *Pakistan Journal of Biotechnology, 13*(3), 173–180.

Saied, N. M., Georgy, G. S., Hussien, R. M., & Hassan, W. A. (2020). Neuromodulatory effect of curcumin on catecholamine systems and inflammatory cytokines in ovariectomized female rats. *Clinical and Experimental Pharmacology and Physiology, 1440–1681*, 13427. https://doi.org/10.1111/1440-1681.13427.

Saklayen, M. G. (2018). The global epidemic of the metabolic syndrome. In *Current Hypertension Reports, 1*Current Medicine Group LLC. https://doi.org/10.1007/s11906-018-0812-z.

Santos-Parker, J. R., Strahler, T. R., Bassett, C. J., Bispham, N. Z., Chonchol, M. B., & Seals, D. R. (2017). Curcumin supplementation improves vascular endothelial function in healthy middle-aged and older adults by increasing nitric oxide bioavailability and reducing oxidative stress. *Aging, 9*(1), 187–205.

Selmanovic, S., Beganlic, A., Salihefendic, N., Ljuca, F., Softic, A., & Smajic, E. (2017). Therapeutic effects of curcumin on ultrasonic morphological characteristics of liver in patients with metabolic syndrome. *Acta Informatica Medica, 25*(3), 169–174. https://doi.org/10.5455/aim.2017.25.169-174.

Shafabakhsh, R., Asemi, Z., Reiner, Ž., Soleimani, A., Aghadavod, E., & Bahmani, F. (2020). The effects of nano-curcumin on metabolic status in patients with diabetes on hemodialysis, a randomized, double blind, placebo-controlled trial. *Iranian Journal of Kidney Diseases, 14*(4), 290–299.

Shang, W., Zhao, L. J., Dong, X. L., Zhao, Z. M., Li, J., Zhang, B. B., & Cai, H. (2016). Curcumin inhibits osteoclastogenic potential in PBMCs from rheumatoid arthritis patients via the suppression of MAPK/RANK/c-Fos/NFATc1 signaling pathways. *Molecular Medicine Reports, 14*(4), 3620–3626. https://doi.org/10.3892/mmr.2016.5674.

Shao, N., Jia, H., Li, Y., & Li, J. (2017). Curcumin improves treatment outcome of Takayasu arteritis patients by reducing TNF-α: A randomized placebo-controlled double-blind clinical trial. *Immunologic Research, 65*(4), 969–974. https://doi.org/10.1007/s12026-017-8917-z.

Shelake, P. S., Yadav, S., Jadhav, M. L., & Dabhi, M. N. (2018). Effect of moisture content on physical and mechanical properties of turmeric (*Curcuma longa*) rhizome. *Current Journal of Applied Science and Technology, 30*(5), 1–7. https://doi.org/10.9734/cjast/2018/44672.

Shirsath, S. R., Sable, S. S., Gaikwad, S. G., Sonawane, S. H., Saini, D. R., & Gogate, P. R. (2017). Intensification of extraction of curcumin from Curcuma amada using ultrasound assisted approach: Effect of different operating parameters. *Ultrasonics Sonochemistry, 38*, 437–445. https://doi.org/10.1016/j.ultsonch.2017.03.040.

Small, G. W., Siddarth, P., Li, Z., Miller, K. J., Ercoli, L., Emerson, N. D., … Barrio, J. R. (2018). Memory and brain amyloid and tau effects of a bioavailable form of curcumin in non-demented adults: A double-blind, placebo-controlled 18-month trial. *American Journal of Geriatric Psychiatry, 26*(3), 266–277. https://doi.org/10.1016/j.jagp.2017.10.010.

Sohaei, S., Amani, R., Tarrahi, M. J., & Ghasemi-Tehrani, H. (2019). The effects of curcumin supplementation on glycemic status, lipid profile and hs-CRP levels in overweight/obese women with polycystic ovary syndrome: A randomized, double-blind, placebo-controlled clinical trial. *Complementary Therapies in Medicine, 47*, Article 102201. https://doi.org/10.1016/j.ctim.2019.102201.

Stewart, J., Manmathan, G., & Wilkinson, P. (2017). Primary prevention of cardiovascular disease: A review of contemporary guidance and literature. *JRSM Cardiovascular Disease, 6*. https://doi.org/10.1177/2048004016687211, 204800401668721.

Thangavel, K., & Dhivya, K. (2019). Determination of curcumin, starch and moisture content in turmeric by Fourier transform near infrared spectroscopy (FT-NIR). *Engineering in Agriculture, Environment and Food, 12*(2), 264–269. https://doi.org/10.1016/j.eaef.2019.02.003.

Wahanik, A. L., Neri-Numa, I. A., Pastore, G. M., Chang, Y. K., & Clerici, M. T. P. S. (2018). Turmeric (*Curcuma longa* L.): New application as source of fiber and antioxidants in pasta with whole wheat flour. *Revista Facultad Nacional de Agronomía Medellín, 71*(1), 8423–8435. Retrieved from http://library1.nida.ac.th/termpaper6/sd/2554/19755.pdf.

Wakte, P. S., Sachin, B. S., Patil, A. A., Mohato, D. M., Band, T. H., & Shinde, D. B. (2011). Optimization of microwave, ultra-sonic and supercritical carbon dioxide assisted

extraction techniques for curcumin from Curcuma longa. *Separation and Purification Technology, 79*(1), 50–55. https://doi.org/10.1016/j.seppur.2011.03.010.
Wang, Q., Ye, C., Sun, S., Li, R., Shi, X., Wang, S., … Liu, R. (2019). Curcumin attenuates collagen-induced rat arthritis via anti-inflammatory and apoptotic effects. *International Immunopharmacology, 72*, 292–300. https://doi.org/10.1016/j.intimp.2019.04.027.
Weisberg, S. P., Leibel, R., & Tortoriello, D. V. (2008). Dietary curcumin significantly improves obesity-associated inflammation and diabetes in mouse models of diabesity. *Endocrinology, 149*(7), 3549–3558. https://doi.org/10.1210/en.2008-0262.
World Health Organization. (2011). Disaster risk management for health fact sheets. Retrieved from http://www.unfpa.org/public/publications/pid/1348.
World Health Organization. (2018). Non-communicable diseases. Retrieved from https://doi.org/10.5005/jp/books/11410_18.
World Health Organization. (2020). Mental health. Retrieved from https://www.who.int/health-topics/mental-health#tab=tab_2.
Yang, C., Wu, K., Li, S. H., & You, Q. (2013). Protective effect of curcumin against cardiac dysfunction in sepsis rats. *Pharmaceutical Biology, 51*(4), 482–487. https://doi.org/10.3109/13880209.2012.742116.
Yang, Y., Duan, W., Lin, Y., Yi, W., Liang, Z., Yan, J., … Jin, Z. (2013). SIRT1 activation by curcumin pretreatment attenuates mitochondrial oxidative damage induced by myocardial ischemia reperfusion injury. *Free Radical Biology and Medicine, 65*, 667–679. https://doi.org/10.1016/j.freeradbiomed.2013.07.007.
Yang, Y. S., Su, Y. F., Yang, H. W., Lee, Y. H., Chou, J. I., & Ueng, K. C. (2014). Lipid-lowering effects of curcumin in patients with metabolic syndrome: A randomized, double-blind, placebo-controlled trial. *Phytotherapy Research, 28*(12), 1770–1777. https://doi.org/10.1002/ptr.5197.
Yusuf, S., Reddy, S., Ôunpuu, S., & Anand, S. (2001). Global burden of cardiovascular diseases. Part I: General considerations, the epidemiologic transition, risk factors, and impact of urbanization. *Circulation, 104*(22), 2746–2753. https://doi.org/10.1161/hc4601.099487.
Zanzer, Y. C., Plaza, M., Dougkas, A., Turner, C., Björck, I., & Östman, E. (2017). Polyphenol-rich spice-based beverages modulated postprandial early glycaemia, appetite and PYY after breakfast challenge in healthy subjects: A randomized, single blind, crossover study. *Journal of Functional Foods, 35*, 574–583. https://doi.org/10.1016/j.jff.2017.06.016.
Zhang, W. Y., Guo, Y. J., Han, W. X., Yang, M. Q., Wen, L. P., Wang, K. Y., & Jiang, P. (2019). Curcumin relieves depressive-like behaviors via inhibition of the NLRP3 inflammasome and kynurenine pathway in rats suffering from chronic unpredictable mild stress. *International Immunopharmacology, 67*, 138–144. https://doi.org/10.1016/j.intimp.2018.12.012.
Zhang, Z., Zhang, R., Zou, L., Chen, L., Ahmed, Y., Al Bishri, W., … McClements, D. J. (2016). Encapsulation of curcumin in polysaccharide-based hydrogel beads: Impact of bead type on lipid digestion and curcumin bioaccessibility. *Food Hydrocolloids, 58*, 160–170. https://doi.org/10.1016/j.foodhyd.2016.02.036.
Zheng, B., Peng, S., Zhang, X., & McClements, D. J. (2018). Impact of delivery system type on curcumin bioaccessibility: Comparison of curcumin-loaded nanoemulsions with commercial curcumin supplements. *Journal of Agricultural and Food Chemistry, 66*(41), 10816–10826. https://doi.org/10.1021/acs.jafc.8b03174.
Žlabur, J.Š., Žutić, I., Radman, S., Pleša, M., Brnčić, M., Barba, F. J., … Voća, S. (2020). Effect of different green extraction methods and solvents on bioactive components of chamomile (*Matricaria chamomilla* L.) flowers. *Molecules, 25*(4), 810. https://doi.org/10.3390/molecules25040810.