TRADITIONAL AND INTEGRATIVE MEDICINE

Trad Integr Med, Volume 9, Issue 2, Spring 2024

Review

Turmeric as a Gut-Microbiota Modulator for Cardio-Metabolic Risk Factors: An Updated Comprehensive Review

Neda Roshanravan[1], Sayyedeh Fatemeh Askari[2], Siavash Fazelian[3], Bahareh Morshed Behbahani[4], Babak Arjmand[5], Nazli Namazi[6]*

[1]Cardiovascular Research Center, Tabriz University of Medical Sciences, Tabriz, Iran
[2]Department of Pharmacognosy and Traditional Pharmacy, School of Pharmacy, Cardiovascular Diseases Research Center, Birjand University of Medical Sciences, Birjand, Iran
[3]Clinical Research Development Unit, Ayatollah Kashani Hospital, Shahrekord University of Medical Sciences, Shahrekord, Iran
[4]Midwifery Department, School of Nursing and Midwifery, Shiraz University of Medical Sciences, Shiraz, Iran
[5]Cell Therapy and Regenerative Medicine Research Center, Endocrinology and Metabolism Molecular-Cellular Sciences Institute, Tehran University of Medical Sciences, Tehran, Iran
[6]Endocrinology and Metabolism Research Center, Endocrinology and Metabolism Clinical Sciences Institute, Tehran University of Medical Sciences, Tehran, Iran

Received: 22 Oct 2023 **Revised:** 25 Mar 2024 **Accepted:** 3 Apr 2024

Abstract

Turmeric is a medicinal herb with antioxidant and anti-inflammatory components that can affect metabolic parameters via various pathways, including the gut-brain axis. Although positive effects of turmeric on health have been reported, findings are conflicting. Accordingly, the current review aimed to provide an overview of the biochemical and biological characteristics of turmeric and examine the impacts of turmeric on cardio-metabolic risk factors with a special focus on its abilities to modulate gut microbiota. In the present comprehensive review, findings of systematic reviews/narrative reviews, clinical trials, animal, and *in vitro* studies on turmeric in the English language published between 2010 and March 2023 were summarized. Findings revealed that turmeric is a safe medicinal herb with mild gastrointestinal side effects in some cases. It can help improve the glycemic status, lipid profile, and blood pressure. However, food processing and fermentation can affect the bioavailability of its effective components, including curcumin. Several mechanisms, including those affecting intestinal microbiota diversity, intestinal permeability, inflammatory and oxidative pathways, are proposed for their positive effects on metabolic factors. However, due to high between-study heterogeneity, limited high-quality clinical trials, differences in the duration of the intervention, and the form of turmeric supplement, more studies on each metabolic parameter are needed to determine effective dosages and confirm its efficacy as a complementary therapy to modulate microbiota and cardio-metabolic parameters.

Keywords: Curcuma; Microbiota; Metabolic diseases; Inflammation

http://doi.org/10.18502/tim.v9i2.15874

Citation: Roshanravan N, Askari SF, Fazelian S, Morshed Behbahani B, Arjmand B, Namazi N. **Turmeric as a Gut-Microbiota Modulator for Cardio-Metabolic Risk Factors: An Updated Comprehensive Review.** Trad Integr Med 2024;9(2):205-218. http://doi.org/10.18502/tim.v9i2.15874

*Corresponding Author: Nazli Namazi
Endocrinology and Metabolism Research Center, Endocrinology and Metabolism Clinical Sciences Institute, Tehran University of Medical Sciences, Tehran, Iran
Email:nazli.namazi@yahoo.com

Copyright © 2024 Tehran University of Medical Sciences. Published by Tehran University of Medical Sciences.This work is licensed under a Creative Commons Attribution-NonCommercial 4.0 International license (https://creativecommons.org/licenses/by-nc/4.0/). Noncommercial uses of the work are permitted, provided the original work is properly cited.

Introduction

Definition and chemical properties

Turmeric (*Curcuma longa* L.) belongs to the family Zingiberaceae which has an intense yellow color and distinct taste. This common spice is derived from the rhizomes, and its name has been applied for almost 4000 years [1]. Turmeric has been utilized over the years in Oriental medicine, the ancient Indian medical system or Ayurveda, Siddha medicine, originating in Southern India, traditional Chinese medicine (TCM), and ancient Greek medicine in the form of traditional medicine [2].

Modern medicine has recently realized the considerable role of turmeric in health [3]. This medicinal herb is rich in natural phytochemicals, containing phenolic compounds from phenylalanine and tyrosine [4]. The major components of turmeric are carbohydrates, fats, proteins, minerals, essential oils, and curcuminoids [5], as yellow polyphenolic pigments from the plant rhizomes and a combination of three non-volatile diarylheptanoids, viz. diferuloylmethane (curcumin I), desmethoxycurcumin (curcumin II), and bisdemethoxycurcumin (curcumin III) [6].

Since ancient times, this medicinal herb has been exploited as a spice in Asian countries for traditional medical purposes [7]. For example, in Persian, it is called *Zard choobe* which enhances the taste and color tonality of rice, yogurt, and chicken [8]. The antioxidant role of turmeric is also attributed to its compounds and volatile oils, particularly curcuminoids [9]. For a long time, turmeric has been further prescribed in Ayurveda to treat indigestion, upper respiratory infection (URI), liver diseases, colds, skin disorders, common burn injuries, and hyperlipidemia [10].

The molecular structure of curcumin, as the principal curcuminoid of turmeric, refers to 1, 7-bis (4-hydroxy-3-methoxyphenyl)-1, 6-heptadiene-3, 5-dione ($C_{21}H_{20}O_6$) (Figure 1) [11]. As concluded by Nabati et al., 208 mg of curcumin could be excreted from 25 g of turmeric powder from the dried ground rhizomes [12].

To realize the functions of turmeric on metabolic status, some explanations of its biological characteristics, medical applications, and main potential mechanisms are provided.

Absorption, metabolism, and bioavailability

The bioavailability of curcumin is poor because of its low absorption in the small intestine [13]. In this way, a wide range of compounds can affect its absorption [14]. The curcumin-binding enterocytes also exacerbate the low bioavailability [15]. On the other hand, lecithin in eggs and plant oils enhances the absorption of curcumin [16]. Recent evidence has indicated that the pharmacokinetics of curcumin in men and women differ because women have much more adipose tissue, and men are endowed

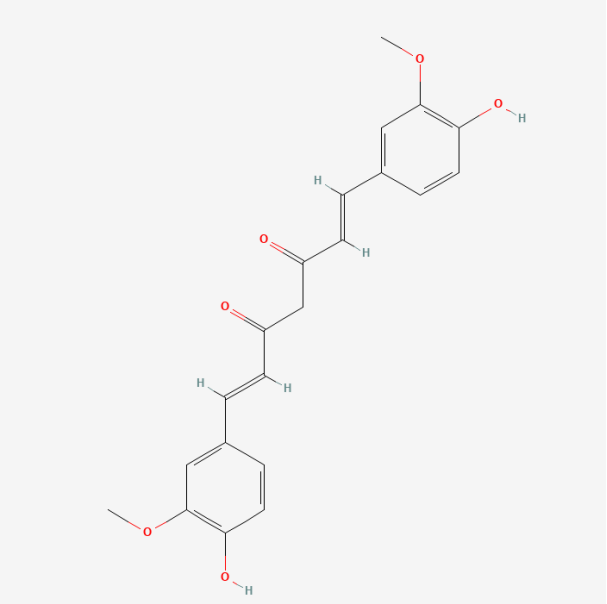

Figure 1. Structure of the curcumin

with higher hepatic clearance [17]. The basic sites of curcumin metabolism are the intestine, the gut microbiota, and the liver [18]. To act as an antioxidant, the reductase cuts the double bonds of curcumin and converts it into di-, tetra-, hexa-, and octa-hydrocurcumin [19].

Application in medicine

Curcumin plays the role of a pleiotropic antioxidant molecule, which can neutralize free radicals leading to the development of chronic diseases, such as atherosclerosis, diabetes mellitus (DM), hypertension (HTN), obesity, and cardiovascular diseases (CVDs) [20]. The protective action of curcumin against most diseases is often fulfilled by modulating the inflammatory transcription factor, nuclear factor-kappa B (NF-κB), cytokines, peroxisome proliferator-activated receptor gamma (PPAR-γ), T helper 2 (Th2) response, cyclooxygenase-2 (COX-2), as well as tumor necrosis factor-alpha (TNF-α). Recent studies have accordingly shown that curcumin can positively affect inflammatory diseases, DM complications, wounds, inflammatory bowel disease (IBD), neurodegenerative conditions, types of cancer, skin problems, allergies, and asthma [21].

Gut microbiota, curcumin, and cardio-metabolic risk factors

Accumulating data support the correlations between the gut microbiota and several risk factors for CVDs including atherosclerosis, dyslipidemia, hypertension, inflammation, obesity, and diabetes mellitus [22]. The human gut microbiota plays a significant role in human metabolic pathways by providing enzymes that are not encoded by the human genome. These enzymes are responsible for breaking down polysaccharides, polyphenols, and

synthesizing vitamins. Two compounds produced by the gut microbiota, trimethylamine N-oxide (TMAO), and short chain fatty acids (SCFA)s, have different effects on the immune system. TMAO has immunomodulatory effects, while SCFAs have pro-inflammatory effects. In high-fat diets, choline and L-carnitine are abundant and are converted into TMA by gut bacteria. The liver then metabolizes TMA into TMAO. TMAO can improve the activation of macrophages, damage the vascular endothelium, and contribute to cardiovascular disease. Dysbiosis, which is an imbalance in the gut microbiota, reduces SCFAs and bile acids, leading to increased intestinal permeability. Heart failure causes congestion in the portal vein, a decrease in cardiac output, reduced intestinal perfusion, and intestinal leakage. These factors result in systemic inflammation by further increasing intestinal leakage. Dysbiosis and increased TMAO levels raise the risk of developing arterial plaque, accelerating the onset of atherosclerosis, and increasing the risk of coronary artery disease. Maintaining a healthy symbiotic relationship between the gut microbiota and the host is crucial for shaping the biochemical profile of the diet. This symbiosis is essential for maintaining the integrity of the intestinal epithelial barrier, promoting the growth of the mucosa, reducing inflammation, and controlling blood pressure [23,24]. In figure 2, the effects of curcumin on gut microbiota have been indicated.

Recent evidence has further indicated the strong link between gut dysbiosis and the circulating levels of gut-derived toxins, oxidative stress, and inflammation [25].

There is growing evidence proposing that the intestinal microbiota plays a significant role in the communication with and impact on the cardiovascular system. This interaction can involve the development of CVDs when the balance of the gut microbiota is disrupted, a condition known as gut dysbiosis. Although the exact mechanisms by which the gut microbiota influences cardiovascular outcomes are not fully understood, it appears that immune dysregulation and disturbances in neuro-enteroendocrine hormones are involved. The disturbances in the gut microbiota can affect the progression of various risk factors for CVDs, such as atherosclerosis, obesity, diabetes, and hypertension. Conversely, these conditions also have an impact on the gut microbiota by compromising the integrity of the intestinal barrier and triggering the release of neurotransmitters and gastrointestinal hormones [26].

Dysbiosis may arise due to various factors specific to the host, including genetic background, health conditions like infections and inflammation, and lifestyle habits. Equally significant are environmental factors such as diet, where a high sugar and low fiber intake can contribute, as well as exposure to xenobiotics like antibiotics, drugs, and food additives. Additionally, hygiene practices also play a role in dysbiosis development [27].

Hyperglycemia, hyperlipidemia, and HTN have been additionally introduced as the major risk factors contributing to the high prevalence rate of cardio-metabolic syndrome (CMS) [28], as one of the public health care priorities of the World Health Organization (WHO) [29]. Over the past decade, genome-wide association (GWA) studies have also revealed the central role of gut microbiota in the CMS [30]. Besides, the use of functional foods for the therapeutic manipulation of luminal microbiota has been extensively investigated in several studies. The positive modulation of the gut microbiota communities is thus one of the most common benefits of some functional ingredients of foods, such as curcumin. As a nutraceutical, curcumin has long been applied for medicinal purposes in Southeast Asia [31].

Current evidence from *in vitro* and animal studies concurs with the therapeutic properties of curcumin in alleviating gut dysbiosis. In a pioneering cell-based survey on the human intestinal epithelial cells, curcumin had thus attenuated hydrogen peroxide (H_2O_2)-induced disruption and restored some H_2O_2-induced changes [32]. Moreover, previous research had suggested that the lipopolysaccharide (LPS)-induced secretion of interleukin-1 beta (IL-1β) and intestinal barrier dysfunction in intestinal epithelial cells could diminish following the implementation of curcumin-based treatments [33]. In another cell line study, Kim further demonstrated that curcumin was able to inhibit the greater permeability of intestinal epithelial barriers in cancer coli-2 (Caco-2) cells induced by IL-1α [34]. Animal models have similarly confirmed the beneficial properties of curcumin to intestinal permeability. According to a previous report, zinc-curcumin supplementation could be effective in the attenuation of gut dysbiosis during doxorubicin-induced cardiomyopathy in rats [35]. In another study, six weeks of nano-bubble curcumin extract administration modulated gut microbiota in male mice [36]. Interestingly, it had been established that curcumin supplementation in cancerous mice could eliminate the tumor burden and subsequently increase bacterial richness and relative abundance of Lactobacillales [37]. In another murine model, curcumin-treated animals have also shown fewer loads of pro-inflammatory enterobacteria and enterococci, but higher loads of anti-inflammatory lactobacilli and bifidobacteria [38].

In a comparable study, the curcumin-based intervention on rats with non-alcoholic fatty liver disease had diminished the serum concentrations of aspartate aminotransferase (AST), alanine aminotransferase (ALT), diamine oxidase (DAO), and TNF-α, as a main inflammatory cytokine [39]. Furthermore, curcumin could have immunomodulatory and tumor-inhibitory activities in the intestinal mucosa, as determined by Churchill et al. [40]. Interestingly, similar animal studies have reported curcumin's anti-inflammatory, immunomodulatory, and antioxidant properties with various doses, that is, 50 mg/kg body weight to 200 mg/kg body weight [41].

The totality of the evidence suggests that gut dysbiosis has been implicated in the development of various car-

dio-metabolic conditions, such as hyperglycemia, DM, hyperlipidemia, and HTN [42]. With various mechanisms, curcumin can thus exert its anti-inflammatory and antioxidant effects, and it is widely recognized for its health-enhancing capacity.

Curcumin's influence on the intestinal microbiota diversity

The regulative effects of curcumin on the gut microbiota communities include microbial richness, diversity, and composition [43]. Based on several studies, a curcumin-supplemented diet can increase the relative abundance of anti-inflammatory lactobacilli and bifidobacteria loads and then decrease the pro-inflammatory enterobacteria and enterococci [44].

Alpha-diversity (α-diversity), as a main indicator for evaluating the gut microbiota health, is thus exploited to describe the microbial diversity of an ecological community [45]. Curcumin can further prevent the reduction in α-diversity in the gut microbiota as a promising predictor of the CMS [46,47].

Curcumin's influence on the intestinal permeability

Many observational studies have so far reported the drop in gut permeability following the practice of curcumin-based treatments [46]. Bacterial lipopolysaccharide (LPS), a well-known cause of the leaky gut phenomenon, also leads to epithelial damage in the gut. LPS with endotoxemia has thus triggered chronic and persistent inflammation in the gut, contributing to DM, hyperlipidemia, HTN, obesity, and the development and progression of types of cancer [47]. Based on *in vitro* studies, LPS could elevate with the increment in the IL-1β expression, which could then activate p38 mitogen-activated protein kinases (MAPKs) and myosin light-chain kinases (MLCKs). The gut permeability could further increase with the phosphorylation of MLCKs, and curcumin-based treatments could lessen the LPS-induced release of IL-1β and moderate the gut permeability [33]. Furthermore, the beneficial properties of curcumin in terms of improvement in the gut permeability could be attributed to the rise in the intestinal alkaline phosphatase activity and tight junction protein expression, including zonula occludens-1 (ZO-1) and claudin-1 (CLDN1) [48].

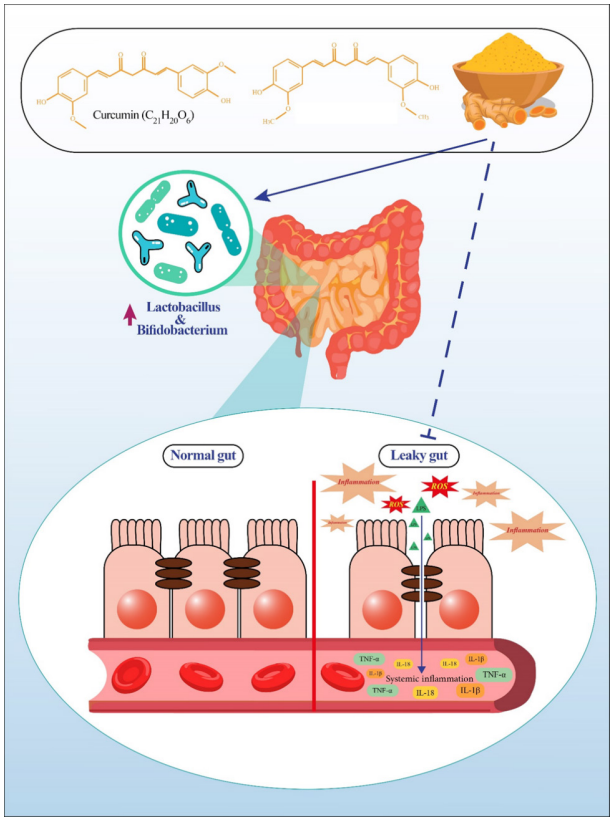

Figure 2- Possible mechanisms of curcumin on gut microbiota

Anti-inflammatory and antioxidant effects of curcumin

Research into gut permeability has further claimed that gut inflammation allows for the translocation of intestinal commensal bacteria and increases gut barrier permeability [49]. Recent data have also suggested that inflammation and impairment in gut barrier function might trigger a series of diseases and health conditions [50]. It has been shown that curcumin administration has been involved in the downregulation of various inflammatory cytokines, such as TNF-α, IL-1β, and IL-6, via inhibiting the activation of the toll-like receptor 4 (TLR4)/NF-κB signaling pathways (viz. the main pathway for releasing the pro-inflammatory cytokine) [51]. Indeed, curcumin could improve gut functions by increasing nitric oxide (NO) bioavailability and reducing oxidative stress [52]. Furthermore, curcumin could exhibit antioxidative properties via the regulation of some signaling pathways, including NF-κB and nuclear factor erythroid-2-related factor 2 (Nrf2, as an important scavenger system in protecting gut from oxidative stress), deoxyribonucleic acid (DNA) methylation, and histone modifications [53]. In clinical trials, curcumin, at a dosage from 90 to 2000 mg/day, has also been effective in modifying gut permeability and reducing inflammation [54].

These mechanisms highlight that curcumin can actively hinder gut inflammation and oxidative stress, and then alleviate some major metabolic disorders, such as DM or atherosclerosis, via the gut-brain axis.

Although the beneficial effects of turmeric and its effective component, curcumin, have been reported, findings are conflicting. To the best of our knowledge, no mechanistic reviews with a holistic view focusing on gut microbiota have been published, so far to summarize the biochemical, biological, and pharmacological effects of turmeric on cardio-metabolic risk factors and intestinal microbiota, which is an interesting and novel target for both prevention and management of metabolic disorders.

Accordingly, the present comprehensive study aimed to (i) overview the biochemical and biological characteristics of turmeric, and (ii) examine the potential mechanisms of turmeric on cardio-metabolic risk factors.

Methodology

In the present comprehensive review, a literature search was performed through PubMed and Scopus databases as well as Google Scholar to identify relevant publications. The latest publications (systematic reviews/ narrative reviews, clinical trials, animal and *in vitro* studies) in the English language on turmeric, not its effective components were collected from 2010 until March 2023. Glycemic status, lipid profile, and blood pressure were considered as primary outcomes. Conference abstracts, case reports, book chapters, editorial letters, theses, and other grey literatures were excluded.

The following sections accordingly summarize the studies in terms of the beneficial effects of turmeric on cardio-metabolic risk factors, such as glycemic status, lipid profile, and blood pressure (BP) at three levels of evidence, i.e., systematic reviews/reviews, clinical trials, as well as animal and *in vitro* studies.

The effects of turmeric on glycemic status

Systematic reviews/ Reviews papers

So far, numerous studies have evaluated the antidiabetic effects of turmeric and its related mechanisms. In a subgroup analysis in a systematic review and meta-analysis by Yuan et al., supplementation with turmeric and curcuminiods could significantly reduce fasting blood glucose (FBG), hemoglobin A1C (HbA1c), fasting serum insulin, and the Homeostatic Model Assessment for insulin resistance (HOMA-IR) index in the patients with metabolic disorders [55].

In a comprehensive review by Zhang et al., the antidiabetic impact of turmeric and its components, especially curcumin, had been linked to various mechanisms, like improving glucose-induced IR via activating the phosphatidylinositol-3-kinase/protein kinase B/glucose transporter 2 (PI3K/Akt/GLUT2) pathway, which had resulted in (i) the upregulation of phosphorylation of the insulin receptor, (ii) insulin receptor substrate (IRS)-1, PI3K, and (iii) Akt, that had finally stimulated the expression of insulin messenger ribonucleic acid (mRNA), increasing the levels of GLUT2 and the activity of glucokinase (GCK), as two essential factors for modulating cellular glucose uptake, metabolism and diminishing OS [56]. In another study, the potential mechanisms of the antioxidant activity of turmeric had been presented as stimulating the Nrf2 signaling pathway through influencing Kelch-like ECH-associated protein 1 (Keap1), the expression of Nrf2 and target genes, the nuclear translocation of Nrf2, and the upstream mediators of Nrf2 [57]. In two other reviews, turmeric had been further associated with postponing DM via improving β-cell functions, preventing β-cell death, and decreasing IR [58, 59]. In addition, Karłowicz-Bodalska et al. had pointed to the modifications in the function of signaling molecules, the level of transcription factors (such as TNF-α), free fatty acid lowering, the activity, as well as lipid peroxidase and lysosomal enzyme inhibition, as the antidiabetic pathways [60].

Clinical trials

In a randomized clinical trial (RCT), turmeric supplementation (500 mg/day, once a day, 60 min before lunch, for four months) by type 2 DM (T2DM) patients also decreased the HOMA-IR index and HbA1c compared to the placebo [61]. In another trial, the effect of a combination treatment containing turmeric and four other medicinal plants (1000 mg/day for eight weeks) was further evaluated in patients with T2DM, reporting a reduction in fasting and post-prandial blood glucose levels, HbA1C, total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), and triglycerides (TG) [62]. An RCT correspondingly investigated the effectiveness of turmeric in the metabolic control of diabetic subjects. The consumption of 500 mg/day of turmeric (with 5 mg of piperine) for 120 days had thus caused a significant reduction in the HOMA index, glycemia, HbA1C, and TG in the turmeric group compared to the controls [63]. Moreover, administering a pill (turmeric extract 125 mg) twice a day for eight weeks in 40 adults with impaired FBG, i.e., between 100 and 125 mg/dL, had attenuated the HOMA-IR index [64]. Uchio et al. had similarly examined the hot-water extract of turmeric (900 mg tablets daily, for 12 weeks) in the overweight or pre-/mild-HTN elderly, and found a significant reduction in the serum levels of glucose, HbA1C, and low-grade inflammation markers, like C-reactive protein (CRP), TNF-α, IL-6, and soluble vascular cell adhesion molecule-1 (sVCAM-1) [65].

Animal and in vitro studies

The antidiabetic potency of turmeric has been further researched in different experimental models. In an animal study by Tebboub et al., the effects of a diet containing 1% turmeric for 4 weeks on diabetic rats fed with a zinc deficiency diet, had been accordingly investigated. They suggested that turmeric could improve decreased body weight, insulin, zinc concentrations in tissues, alkaline phosphatase (ALP), glutathione, glutathione peroxidase (GPX), superoxide dismutase (SOD), catalase (CAT), as well as increased glucose, lipid profile, transaminases, and malondialdehyde (MDA) in rats with zinc deficiency. Of note, zinc is a valuable antioxidant with a critical role in insulin synthesis. This study reported that turmeric could modulate the consequences of zinc deficiency related to DM [66]. In another study, the antidiabetic effect of intraperitoneal turmeric (250 mg/kg twice weekly) and

oral curcumin (500 mg daily) for 4 weeks was examined in streptozotocin (STZ)-induced diabetic rats. Both treatments had thus caused a reduction in glucose levels and improved TC and islet cell protection due to the antioxidant activity of turmeric, which could inhibit cell apoptosis, but in high doses, could disturb the liver enzymes. It was further uncovered that turmeric and its components had ameliorated renal functions by decreasing serum creatinine and blood urea concentrations via decreasing transforming growth factor-beta (TGF-β) and IL-8. The beneficial effects on serum lipids were also related to the induction of PPAR-γ function connected to adipogenesis and the normalization of antioxidant parameters involved in glucose and lipid metabolism, including MDA, SOD, and GPX [67]. In line with this study, El-Hadary et al. showed the positive effects of turmeric (200 mg /kg of hydroalcoholic extract for 56 days), on antioxidant and anti-inflammatory parameters, which could be involved in its antidiabetic effects. Moreover, turmeric causes insulin secretion to prevent the destructive effect on pancreas β-cells and reduces matrix metalloproteinases in the liver damage [68].

Taking turmeric and resistance training further elevated body weight recovery, reduced serum glucose, and decreased reactive species markers in serum, pancreas, skeletal muscle, and cardiac tissues induced by T1DM. These advantages might thus improve GLUT-4 translocation, reactive oxygen species (ROS) production, creatine kinase (CK), ALT, uric acid, and thiobarbituric acid reactive substance (TBARS) levels [69]. This study performed in male Wistar diabetic rat model that received 200 mg/kg turmeric, 3 times a week, for 4 weeks orally. A multi-ingredient decoction tested in mice for 8 weeks, and its sound effects on FBS and related markers had further affected diabetic nephropathy via the reduction in serum TGF-β1 levels and the downregulation of the expression of hypoxia-inducible factor-1α (HIF-1α), vascular endothelial growth factor (VEGF), and TGF-β1 at both mRNA and protein concentrations [70]. The role of turmeric in preventing and decreasing DM-induced complications had been also confirmed in a study by Margia et al. Notably, the main components of turmeric are phenolics, like ferulic, gallic, and caffeic acids, responsible for antioxidant effects, as assessed by the 2,2-diphenyl-1-picrylhydrazyl (DPPH) assay and the membranes of lipid peroxidation Jurkat cells. Turmeric remarkably reduced intercellular adhesion molecule-1 (ICAM-1) level in the cell medium, similar to curcumin solution [71]. Nishamalaki (NA), is an Indian formulation containing *Phyllanthus emblica* and *Curcuma longa*. It presents antidiabetic, antihyperlipidemic, and preventive effects against diabetic neuropathy by the hot-water tail immersion test unit, assessment of cold allodynia, and sciatic nerve antioxidant activity through the MDA reduction, leading to the prevention of lipid peroxidation, SOD, and CAT augmentation, which had resulted in a decrement in the production of superoxide radical in male diabetic mice for 12 weeks. Furthermore, NA had the desirable penetration inside the nerves because the antioxidant activity was observed in the neuronal tissue [72]. Besides, 1000 mg/kg of NA for 4 weeks lowered the elevated blood glucose and insulin levels, resulting in IR amelioration in the STZ- and high-fat diet-induced T2DM rats. In this study, the positive effects of turmeric had been mentioned, like growth in PI3K-Akt-glycogen synthase kinase 3 beta (GSK3β) signal and a decrease in the phosphorylation of the extracellular signal-regulated kinase/c-Jun N-terminal kinase (ERK/JNK) in hepatocytes, leading to a decrement in IR and an increment in the insulin sensitivity of the cells [73]. Other studies have also confirmed the positive effects of turmeric in combination with other medicinal herbs on glucose and lipid metabolism, IR, and HbA1C in diabetic and obese animal models [74]. As evidenced, supplementation with turmeric could be generally helpful in improving glycemic status in both patients with DM and other glycemic disorders.

The effects of turmeric on lipid profile

Systematic reviews/ Reviews papers

In a meta-analysis of RCTs, Qin et al. had further addressed the possible mechanisms of turmeric and curcumin concerning lipid-lowering effects in cardiovascular complications. They had accordingly reported enhanced effects on serum lipid levels, i.e., reduced serum LDL-C, TG, and TC (especially in patients with metabolic disorders), but no remarkable changes in HDL-C following turmeric use. The interesting point is that the antihyperlipidemic effects of turmeric and its components will be explicit just in CVDs, like metabolic disorders, T2DM, and obesity through binding to PPAR-γ, with a preventive role in suppressing the expression of the LDL-C receptor gene, and thereby reducing plasma LDL-C levels [75].

Another systematic review and meta-analysis correspondingly revealed the modulating effect of turmeric on TG, TC, LDL-C, and HDL-C in adults with metabolic disorders via a regulatory effect on lipid metabolism and cellular transduction pathways, which are essential in metabolic disorders. The inhibitory effects on the expression of lipogenic factors had then reduced the TG and TC levels [76]. In this way, Dosoky et al. had concentrated on turmeric essential oil mechanisms of actions related to the antihyperlipidemic effects, such as the inhibition of α-glucosidase and α-amylase activities, antioxidant activity compared to metal-chelating activity assay, ferric reducing/antioxidant power (FRAP) assay, 1,1-diphenyl-2-picrylhydrazyl (DPPH) radical scavenging activity assay, and superoxide anion radical scavenging activity assay [77].

Turmeric, as a common spice, plays different roles in managing hyperlipidemia, as discussed in a review article by Zhao et al. (2018), including improving he-

patic cholesterol homeostasis, downregulating 3-hydroxy-3-methyl-glutaryl-CoA reductase (HMG-CoA-R) gene expression (caused by an interruption in cholesterol synthesis), activating cytochrome P450 family 7 subfamily A member 1 (CYP7A1) (eliminated cholesterol in the liver via the fecal excretions of bile acids), upregulating AMP-activated protein kinase (AMPK) and PPARα (enhanced fatty oxidation), downregulating sterol regulatory element-binding protein 1c (SREBP1c), acetyl CoA carboxylase (ACC), fatty acid synthase (FAS) (inhibited lipogenesis), and finally, downregulating the expression of sterol regulatory element-binding protein 2 (SREBP2) (inhibited absorption of cholesterol in the small intestine) [78].

Clinical trials

In a randomized, double-blinded, placebo-controlled, parallel study, turmeric intake (2100 mg/day for eight weeks) by hyperlipidemic T2DM patients had attenuated body weight, TG, and LDL-C in comparison with the placebo [79]. The supplementation with turmeric also decreased TG compared to the placebo in patients with T2DM [61]. In another trial, the consumption of a formulation containing turmeric in T2DM patients had diminished serum TC, LDL-C, and TG, but increased HDL-C [62]. Moreover, the administration of a combined medicine (turmeric extract 125 mg) improved TG and HDL-C with no effect on LDL-C [64]. In this respect, Amin et al. designed an RCT to evaluate turmeric's efficacy of turmeric (800 mg) in combination with *Nigella sativa* (300 mg+50 mg turmeric) by taking one capsule three times a day for eight weeks in healthy males screened positive for metabolic syndrome. After eight weeks of intervention, LDL-C and CRP had demoted following taking turmeric. Compared with the placebo, the combined formulation had improved body fat percentage (BF%), FBS, TG, LDL-C, HDL-C, and CRP concentrations [80].

LI85008F, as an herbal blend containing turmeric and two other extracts, had shown promising effects on fat and lipids levels in overweight participants. After the consumption of 900 mg/day of capsules in two divided doses for 16 weeks, a reduction had been seen in body weight, BMI, waist and hip circumferences, waist/hip ratio, and LDL-C, and there were improvements in the HDL-C and LDL/HDL ratios without any adverse effects [81]. According to Ghaffari et al., turmeric (3 g/day) in combination with chicory seed (9 g+3 g turmeric/ day) for 12 weeks in non-alcoholic fatty liver disease (NAFLD) patients had reduced BMI, waist circumference, TG/HDL-C, LDL-C/HDL-C ratio, and consequently improved HDL-C [82]. Another study in overweight or pre-HTN participants had further exhibited a fall in TG and a rise in HDL-C compared with the placebo group [65]. Another mixed natural supplement, Kepar, containing 160 mg turmeric, had been correspondingly evaluated in 78 participants with metabolic syndrome as adjuvant therapy. After four months of intervention (2 pills/day), significant reductions had been observed in body weight, BMI, waist circumference, FBS, and TC [83].

Animal and in vitro studies

In a study by El-Hadary et al. (2020), 200 mg/kg turmeric hydroalcoholic extract for 56 days had improved lipid profile, including TC, TG, HDL-C, and very-low-density lipoprotein (VLDL) in diabetic rats. Turmeric had also reversed the pathways leading to dyslipidemia, such as the promotion of HMG-CoA-R along with the immobilization of free fatty acids, fat absorption, and excretion [68]. In another study, the consumption of turmeric and resistance training had attenuated the serum levels of cholesterol compared to diabetic control group rats. A reduction in the ROS markers in different tissues might have thus led to such an effect [69]. As evidenced significant reversion in SOD, GPX, CAT, TC, HDL-C, LDL-C, TG, MDA, leptin (as a representative of lipid accumulation in visceral tissues induced by high-fat diet), and liver enzymes (like AST and ALT, which had increased under the influence of hypercholesterolemia) had been observed following turmeric supplementation (2 mg/day of turmeric in combination with other herbs for 30 days in hypercholesterolemic mice). Based on strong evidence, the synergistic effects of combined herbs, especially turmeric, because of its curcumin and polyphenols, had led to the inhibition of HMG-CoA reductase and the reduction in liver cholesterol biosynthesis [84]. In the research by Zhou, all formulations containing turmeric administered to obese mice, for 4 weeks, had further exhibited a dwindling effect on lipid levels and their accumulation, the regulatory activity of adipocytokines, and the lipid metabolism gene expression, which had led to the gut microbiota balance. Other possible mechanisms are the inhibition of α-glucosidase and pancreatic lipase activities, the reduction in adipose tissue, and the attenuation of FAS and SREBP-1c gene expression (responsible for liver lipid synthesis) [85].

In general, the cardioprotective and antihyperlipidemic effects of turmeric might be due to the anti-inflammatory and antioxidant activities of the main component, i.e., curcumin that helps regulate the pathways, such as NF-κB, nuclear factor erythroid 2-related factor 2-Kelch-like ECH-associated protein 1 (Nrf2-Keap1), and MAPK. Moreover, attenuation in the LDL-C, TG, CRP, and LDL receptors caused more LDL uptake. The suspension of intracellular cholesterol aggregation in macrophages has been reported as another mechanism of turmeric in CVDs [56].

The effects of turmeric on blood pressure

Systematic reviews/ Reviews papers

Characterized by antioxidant/anti-inflammatory activity, calcium (II) ion concentration interference, β2-adrener-

gic receptor activation, and renin-angiotensin system inhibition, turmeric could also control BP [86]. Mechanistically, curcumin and its analogs, like hexahydrocurcumin and tetrahydrocurcumin, can have an antihypertensive effect through diverse signaling pathways, viz., pathways mediated by Nrf2-antioxidant response element (ARE), NF-κB, NO/ cyclic guanosine monophosphate (cGMP)/ phosphodiesterase type 5 (PDE5)/matrix metalloproteinases (MMPs), renin-angiotensin-aldosterone system/ angiotensin-converting enzyme (RAAS/ACE), histone acetyltransferase/histone deacetylase (HAT/HDAC), G0/G1/apoptosis, cytochrome P450 3A4 (CYP3A4), mitochondrial uncoupling protein 2/ poly (ADP-ribose) polymerase (UCP2/PARP), VEGF/ signal transducer and activator of transcription (STAT)/AXL/tyrosine kinase, and TGF-β/Smad-mediated pathways [87]. Given its anti-inflammatory and antioxidant properties, curcumin could have antihypertensive effects by increasing NO in metabolic syndromes [88]. Studies with ≥ 12 weeks of curcumin/turmeric supplementation have thus suggested that curcumin/turmeric consumption might improve systolic BP (SBP) if administered in the long term [89].

Clinical trials, animal and in vitro studies

The insolubility of turmeric in water and its low biological impact on therapeutic uses have further led scientists to consider the use of nanoparticles (NPs). Curcumin's NPs accordingly provide a possible plan for the sustained delivery of curcumin in a discovery phase. Therefore, bioavailability and efficiency are improved. Nanomedicine also bridges the gap between drug limitations and the therapeutic potential of curcumin by enhancing the pharmacokinetic efficacy and cellular uptake of curcumin [90]. Despite these results, a new study suggested that the consumption of the NPs at a dose of 1×58 mg (4-gram dose) had been effective in lowering BP and lipid profile (viz. TC, HDL-C, LDL-C, and TG) in patients with hypercholesterolemia [91]. However, all studies have not confirmed this. In this respect, Bateni et al. had concluded that the nano-curcumin supplementation of 80 mg/day for 12 weeks had not resulted in lowering BP in patients with metabolic syndromes [92].

Curcumin could further reduce elevated SBP and prevent aorta-exaggerated response to phenylephrine and potassium chloride (KCl) in DM-evoked hypertensive rats. It could be further developed to inhibit the proliferation and migration of vascular smooth muscle cells (VSMCs) through various signaling pathways. Dehydrozingerone, a structural analog of curcumin, could also induce a dose-dependent inhibition of platelet-derived growth factor (PDGF)-stimulated VSMC migration, proliferation, and collagen synthesis via inhibiting the phosphorylation of PDGF-receptor (PDGFR) and Akt. It might be used as a dietary supplement to antagonize HTN and its associated vascular dysfunction by suppressing vascular inflammation and OS, restoring eNOS/NO signaling, reshaping the gut microbial composition, and inhibiting p300-HAT activity [90]. Additionally, combined administration of 30% ethanol and aqueous extracts of curcumin with amlodipine could induce a stronger vasorelaxant effect than amlodipine alone. However, this administration had not significantly decreased BP compared with single amlodipine [93]. These benefits were more common in the cases of HTN due to inflammation and vascular dysfunction than genetic diseases.

In patients with DM, curcumin could have a regulatory role in cardio-metabolic disease-associated vascular dysfunction by attenuating the phenylephrine-induced increase in contraction during the early stage of the STZ-induced conditions [90]. Central arterial stiffness and endothelial dysfunction in DM could accordingly increase the risk of CVDs and HTN. In such patients, 400 mg TDS/day of *Curcuma longa* after three months of treatment had significantly lowered arterial stiffness compared with the placebo [94].

In patients with relapsing or refractory biopsy-proven lupus nephritis, one capsule for three months, which contained 500 mg turmeric, had further decreased proteinuria, hematuria, and SPB [95]. The turmeric-based therapy of 3,000 mg/day of turmeric powder in six 500-mg capsules for 12 weeks in patients with NAFLD had thus reduced SBP [96]. Nevertheless, Nowak et al. emphasized that oral curcumin therapy would not diminish vascular endothelial dysfunction and arterial stiffness in children and young adults with autosomal dominant polycystic kidney disease (ADPKD) [97].

Turmeric and many of its derivatives could also reduce HTN *in vitro* and in animal studies via ACE inhibition and arteriole vasodilation. The potentiation of NO donor activity has been also identified as a probable mechanism for the vasorelaxation activity [98]. It has been indicated that turmeric could decrease BP in mice with HTN [99]. One major metabolite of curcumin, hexahydrocurcumin, could further have antihypertensive actions by inhibiting vascular inflammation and oxidative stress, as well as activating the eNOS/NO pathway in aortic tissues in experimental animal models. Therefore, it could prevent the elevation of BP, and diminish the increased wall thickness [100]. Overall, although there is evidence on the positive effects of turmeric on SBP and a number of studies have revealed some underlying mechanisms, more clinical trials are needed to confirm its efficacy.

In figure 3, possible mechanisms by which curcumin affects glycemic status, lipid profile, and blood pressure have been summarized.

Effects of food processing on the content and stability of turmeric

Food processing and macronutrients can further affect curcumin bioavailability [101]. Several compounds can accordingly influence further absorption, longer circulation, and better permeability of turmeric and curcumin

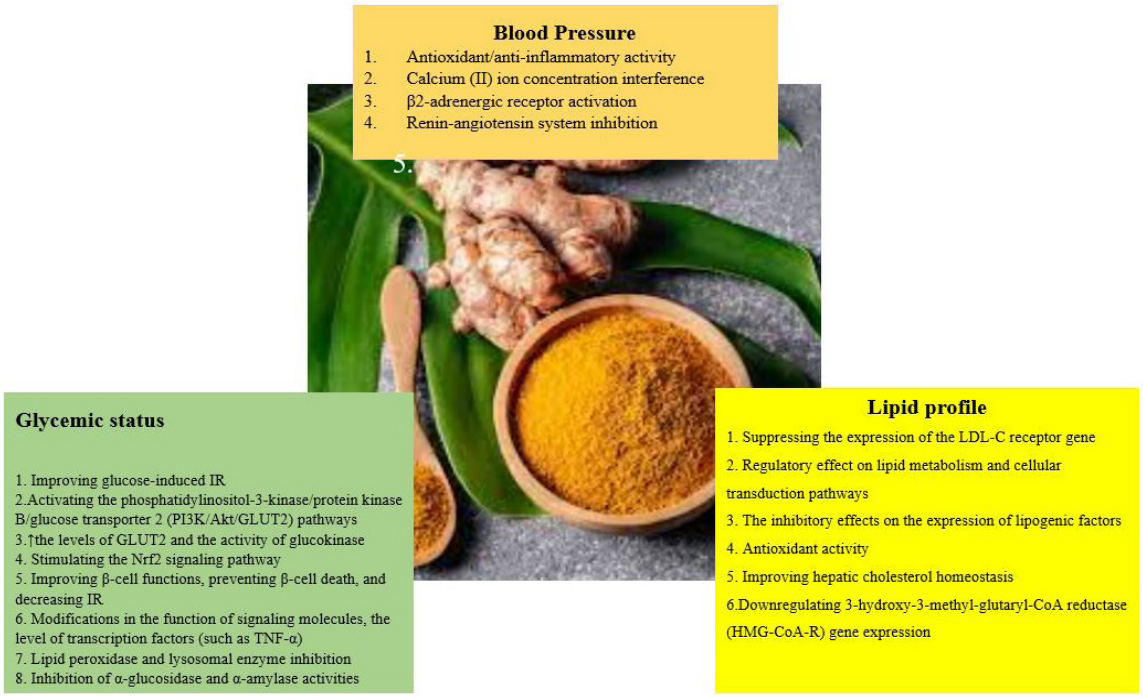

Figure 3. Possible mechanisms of curcumin on metabolic disorders
IR: Insulin Resistance, PI3K/Akt/GLUT2: phosphatidylinositol-3-kinase/protein kinase B/glucose transporter 2, Nrf2: nuclear factor erythroid 2–related factor 2, TNF-α: Tumor Necrosis Factor-alpha, LDL-C: Low-Density Lipoprotein Cholesterol

[102]. The best conditions for drying turmeric are temperature of 70 °C and in the presence of polycarbonate. In this case, drying time is shorter and dyes and curcuminiods are better preserved [103]. A recent study had thus shown that fermented turmeric had better bioavailability, which was consistent with the concentration of polyphenolic compounds in rats [104]. Effective ways to enhance absorption during cooking could be using a source of fat (such as avocado, nut butter, nuts, fish, etc.) and black pepper [105].

Applications in the industry

Generally, the absorption of curcumin is low and nanotechnology can increase the bioavailability in the body. If supplementation with curcumin is expected to decrease OS, its absorption must be increased in the pharmaceutical industry by incorporating agents like piperine to boost bioavailability and build a curcumin complex [101]. Turmeric is further used in curry spices and as a hot beverage in Korea and Japan [106], applied as an antiseptic in Malaysia and an anti-inflammatory substance in India and Pakistan, and as mustard sauce and an ingredient in cheese, butter, and chips in the United States [106]. There are several dosage forms of curcumin, including tablets, powders, and capsules, mainly available on the market to reduce inflammation, pain, and bacterial infections [107]. The United States Food and Drug Administration (FDA) also introduced turmeric as a safe product that provides a range from 4000 to 8000 mg [108].

Side effects and toxicology

Human and animal studies indicated that turmeric (or its major constituent, curcumin) has no toxic or teratogenic effect. They have been widely used for therapeutic cases and as a spice in foods. Still, it is not on any readily accessible U.S. Food and Drug Administration (FDA) and GRAS (generally recognized as safe) list-2016 [109,110]. The safe dosage of curcumin for oral use in various studies is between 8 to 12 g per day for a healthy person for three months [111-115]. Intravenous formulations of curcumin have greater absorption. Therefore, it should be administered at lower doses than oral use [116]. Several studies have reported minor side effects if high doses are used [114,117-119].

Adverse effects in the gastrointestinal tract are diarrhea, bad taste, hepatotoxicity, nausea, gastric irritation, gallbladder problems, gastrointestinal discomfort, dyspepsia, abdominal pain, constipation, stimulating gallbladder contractions, flatulence, and exacerbating symptoms in patients with gallstones [115,120]. Curcumin supplementation of 20-40 mg has been reported to increase gallbladder contractions in healthy people. Animal studies have reported an increase in liver weight, discolored faces, and hyperplasia of the cecum and colon. [111,113-118,120-124]. Oral use of turmeric may prevent Iron absorption. Therefore, it should be used with caution in subjects with iron deficiency [124].

Other studies reported these adverse effects of curcumin on the reproductive system. Ovarian follicle development

suppuration by the 7% and 5% turmeric-supplemented diet in one animal study was reported [125]. *Curcuma zedoaria* decreases the motility and viability of spermatozoa in mice [126]. Turmeric can cause uterine stimulation and increase bleeding [11] and it increases uterine contraction in pregnant women. A high dose of turmeric causes lower testosterone and decreased sperm movement in a human study [124,127].

Headache, hypersensitivity, and vertigo are other minor side effects of turmeric [111,120-121]. Turmeric contains 2% oxalate, hence high doses can lead to kidney stone formation [10]. Some studies have reported skin problems, local, reversible allergic dermatitis, skin rashes, swollen skin, allergic contact dermatitis, itching, tongue redness, and tachycardia by oral use of curcumin [114,116,117].

Turmeric has antiplatelet effects *in vitro*, but it has not been demonstrated *in vivo*, and no adverse effects or interactions have been so far reported in clinical trials or case reports. Some studies have also shown that turmeric reduces the levels of white and red blood cells [127].

Curcumin can further interact with some medications, such as antiplatelet, camptothecin, mechlorethamine, doxorubicin, cyclophosphamide, celiprolol, midazolam, and tacrolimus [128]. It may also give rise to pharmacokinetic changes in cardiovascular medications, antibiotics, antidepressant agents, chemotherapeutic drugs, anticoagulants, and antihistamines [116,123].

Conclusion

From the clinical point of view, turmeric (1-3 g/day of powder) as a supplement along with conventional therapies can lead to low-to-moderate improvement in metabolic parameters which play key roles in the occurrence of cardiovascular diseases. In general, its effects in patients with metabolic disorders such as those with diabetes, dyslipidemia, and metabolic syndrome are greater than other cases. The beneficial effects of this medicinal herb can be exerted via various pathways involved in controlling each metabolic parameter. However, affecting inflammatory and oxidative pathways, as well as the modulation of gut microbiota are the main possible mechanisms that are proposed for turmeric and its main components to control glycemic status, lipid profile, and blood pressure based on both experimental studies and clinical trials. However, due to limited high-quality clinical trials, between-study heterogeneity, and differences in methodologies (design, dosages, duration of the intervention, form of turmeric, etc.,), its efficacy and effective dosage for any metabolic disorders remained uncovered. Although most studies reported higher dosages of turmeric that are usually applied for cooking, it should be kept in mind that food processing, particularly fermentation, and consumption with oil, can increase the bioavailability of turmeric's effective components. Moreover, turmeric is safe and has no severe adverse effects based on the available evidence. All in all, as the present study attempted to draw an overview of clinical applications of turmeric with a focus on potential mechanisms particularly the modulation of gut flora, drawing a certain conclusion about its efficacy and effective dosage was not possible and the conclusion must be provided by caution. In the future, high-quality clinical trials on turmeric focusing on gut microbiota as an outcome in patients at risk for cardiovascular diseases are proposed.

Conflict of Interests

None.

Acknowledgments

None.

References

[1] Fabianowska-Majewska K, Kaufman-Szymczyk A, Szymanska-Kolba A, Jakubik J, Majewski G, et al. Curcumin from turmeric rhizome: a potential modulator of DNA methylation machinery in breast cancer inhibition. Nutrient 2021;13:332.

[2] Awuchi CG. Medicinal plants: the medical, food, and nutritional biochemistry and uses. Int J Adv Acad Res 2019;5:220-241.

[3] Akaberi M, Sahebkar A, Emami SA. Turmeric and Curcumin: From Traditional to Modern Medicine. Studies on Biomarkers and New Targets in Aging Research in Iran: Springer. 2021; pp 15-39.

[4] Wojno M, Mandas A, Kwasek K, Dabrowski K. The effect of dietary supplements of black pepper piper nigrum and turmeric curcuma longa extracts on dietary amino acid utilization and growth performance in common carp. N Am J Aquac 2021;83:155-164.

[5] Jayashree E, Zachariah TJ, Rakhi R. Comparison of quality of dry turmeric (Curcuma longa) produced by slicing and other curing methods. J Spices Ar Crops 2018;27:138-144.

[6] Amalraj A, Pius A, Gopi S, Gopi S. Biological activities of curcuminoids, other biomolecules from turmeric and their derivatives–A review. J Trad Complement Med 2017;7:205-233.

[7] Gopinath H, Karthikeyan K. Turmeric: a condiment, cosmetic and cure. Indian J Dermatol Venereol Leprol 2018;84:16-21.

[8] Ahmad RS, Hussain MB, Sultan MT, Arshad MS, Waheed M, et al. Biochemistry, safety, pharmacological activities, and clinical applications of turmeric: a mechanistic review. Evid Based Complement Alternat Med 2020;2020:7656919.

[9] Akter J, Hossain MA, Takara K, Islam MZ, Hou D-X. Antioxidant activity of different species and varieties of turmeric (Curcuma spp): Isolation of active compounds. Comp Biochem Physiol C Toxicol Pharmacol 2019;215:9-17.

[10] Chanda S, Ramachandra T. Phytochemical and pharmacological importance of turmeric (Curcuma longa): A review. Res Rev A J Pharmacol 2019;9:16-23.

[11] Sharifi-Rad J, Rayess YE, Rizk AA, Sadaka C, Zgheib R, et al. Turmeric and its major compound curcumin on health: bioactive effects and safety profiles for food, pharmaceutical, biotechnological and medicinal applications. Front Pharmacol 2020;11:01021.

[12] Nabati M, Mahkam M, Heidari H. Isolation and characterization of curcumin from powdered rhizomes of turmeric plant marketed in Maragheh city of Iran with soxhlet technique. Iran Chem Commun 2014;2:236-243.

[13] Liu Z, Smart JD, Pannala AS. Recent developments in formulation design for improving oral bioavailability of curcumin: a review. J Drug Deliv Sci Technol 2020;60:102082.
[14] Sanidad KZ, Sukamtoh E, Xiao H, McClements DJ, Zhang G. Curcumin: recent advances in the development of strategies to improve oral bioavailability. Annu Rev Food Sci Technol 2019;10:597-617.
[15] Cozzolino M, Delcanale P, Montali C, Tognolini M, Giorgio C, et al. Enhanced photosensitizing properties of protein bound curcumin. Life Sci 2019;233:116710.
[16] Dei Cas M, Ghidoni R. Dietary curcumin: correlation between bioavailability and health potential. Nutrients 2019;1:2147.
[17] Chen S, Li Q, Li H, Yang L, Yi J-Z, et al. Long-circulating zein-polysulfobetaine conjugate-based nanocarriers for enhancing the stability and pharmacokinetics of curcumin. Mater Sci Eng C 2020;109:110636.
[18] Kunihiro AG, Brickey JA, Frye JB, Luis PB, Schneider C, et al. Curcumin, but not curcumin-glucuronide, inhibits Smad signaling in TGFβ-dependent bone metastatic breast cancer cells and is enriched in bone compared to other tissues. J Nutr Biochem 2019;63:150-156.
[19] Mirzaei M, Harismah K, Soleimani M, Mousavi S. Inhibitory effects of curcumin on aldose reductase and cyclooxygenase-2 enzymes. J Biomol Struct Dyn 2021;39:6424-6430.
[20] Gupta SC, Prasad S, Kim JH, Patchva S, Webb LJ, et al. Multitargeting by curcumin as revealed by molecular interaction studies. Nat Prod Rep 2011;28:1937-1955.
[21] Kocaadam B, Şanlier N. Curcumin, an active component of turmeric (Curcuma longa), and its effects on health. Crit Rev Food Sci Nutr 2017;57:2889-2895.
[22] Hemmati M, Kashanipoor S, Mazaheri P, Alibabaei F, Babaeizad A, et al. Importance of gut microbiota metabolites in the development of cardiovascular diseases (CVD). Life Sci 2023;329:121947.
[23] Xu H, Wang X, Feng W, Liu Q, Zhou S, et al. The gut microbiota and its interactions with cardiovascular disease. Microb Biotechnol 2020;13:637-656.
[24] Kazemian N, Mahmoudi M, Halperin F, Wu JC, Pakpour S. Gut microbiota and cardiovascular disease: opportunities and challenges. Microbiome 2020;8:1-17.
[25] Katiraei S. Role of intestinal microbiota in cardio-metabolic diseases. [Doctoral Thesis]: Leiden University. [2023].
[26] Sata Y, Marques FZ, Kaye DM. The emerging role of gut dysbiosis in cardio-metabolic risk factors for heart failure. Curr Hypertens Rep 2020;22:1-8.
[27] Hrncir T. Gut microbiota dysbiosis: triggers, consequences, diagnostic and therapeutic options. Microorganisms 2022;10:578.
[28] Letswalo BP, Schmid-Zalaudek K, Brix B, Matjuda EN, Klosz F, et al. Cardiometabolic risk factors and early indicators of vascular dysfunction: a cross-sectional cohort study in South African adolescents. BMJ Open 2021;11:e042955.
[29] Verhaar BJH, Prodan A, Nieuwdorp M, Muller M. Gut Microbiota in Hypertension and Atherosclerosis: A Review. Nutrients 2020;12:2982
[30] Karlsson FH, Fåk F, Nookaew I, Tremaroli V, Fagerberg B, et al. Symptomatic atherosclerosis is associated with an altered gut metagenome. Nat Commun 2012;3:1245.
[31] Ghaffari S, Roshanravan N. The role of nutraceuticals in prevention and treatment of hypertension: An updated review of the literature. Food Res Int 2020;128:108749.
[32] Wang N, Wang G, Hao J, Ma J, Wang Y, et al. Curcumin ameliorates hydrogen peroxide-induced epithelial barrier disruption by upregulating heme oxygenase-1 expression in human intestinal epithelial cells. Dig Dis Sci 2012;57:1792-1801.
[33] Wang J, Ghosh SS, Ghosh S. Curcumin improves intestinal barrier function: modulation of intracellular signaling, and organization of tight junctions. Am J Physiol Cell Physiol 2017;312:C438-445.
[34] Kim CY. Inhibition of interleukin-1α-induced intestinal epithelial tight junction permeability by curcumin treatment in Caco-2 Cells in Caco-2 cells. J Life Sci 2016;26:1082-1087.
[35] Wu R, Mei X, Wang J, Sun W, Xue T, et al. Zn(ii)-Curcumin supplementation alleviates gut dysbiosis and zinc dyshomeostasis during doxorubicin-induced cardiotoxicity in rats. Food Funct 2019;10:5587-5604.
[36] Chen YM, Chiu WC, Chiu YS, Li T, Sung HC, et al. Supplementation of nano-bubble curcumin extract improves gut microbiota composition and exercise performance in mice. Food Funct 2020;11:3574-3584.
[37] McFadden RM, Larmonier CB, Shehab KW, Midura-Kiela M, Ramalingam R, et al. The Role of curcumin in modulating colonic microbiota during colitis and colon cancer prevention. Inflamm Bowel Dis 2015;21:2483-2494.
[38] Bereswill S, Muñoz M, Fischer A, Plickert R, Haag LM, et al. Anti-inflammatory effects of resveratrol, curcumin and simvastatin in acute small intestinal inflammation. PLoS One 2010;5:e15099.
[39] Hou HT, Qiu YM, Zhao HW, Li DH, Liu YT, et al. Effect of curcumin on intestinal mucosal mechanical barrier in rats with non-alcoholic fatty liver disease. Zhonghua Gan Zang Bing Za Zhi 2017;25:134-138.
[40] Churchill M, Chadburn A, Bilinski RT, Bertagnolli MM. Inhibition of intestinal tumors by curcumin is associated with changes in the intestinal immune cell profile. J Surg Res 2000;89:169-175.
[41] Long L, Wang J, Chen N, Zheng S, Shi L, et al. Curcumin ameliorates reserpine-induced gastrointestinal mucosal lesions through inhibiting IκB-α/NF-κB pathway and regulating expression of vasoactive intestinal peptide and gastrin in rats. J Med Food 2016;19:528-534.
[42] Shen L, Ji HF. Intestinal microbiota and metabolic diseases: pharmacological implications. Trends Pharmacol Sci 2016;37:169-171.
[43] Cryan JF, O'Riordan KJ, Sandhu K, Peterson V, Dinan TG. The gut microbiome in neurological disorders. Lancet Neurol 2020;19:179-194.
[44] Song W-B, Wang Y-Y, Meng F-S, Zhang Q-H, Zeng J-Y, et al. Curcumin protects intestinal mucosal barrier function of rat enteritis via activation of MKP-1 and attenuation of p38 and NF-κB activation. PloS One 2010;5:e12969.
[45] Tian S, Guo R, Wei S, Kong Y, Wei X, et al. Curcumin protects against the intestinal ischemia-reperfusion injury: involvement of the tight junction protein ZO-1 and TNF-α related mechanism. Korean J Physiol Pharmacol 2016;20:147-152.
[46] Ghosh SS, Bie J, Wang J, Ghosh S. Oral supplementation with non-absorbable antibiotics or curcumin attenuates western diet-induced atherosclerosis and glucose intolerance in LDLR−/− mice–role of intestinal permeability and macrophage activation. PloS One 2014;9:e108577.
[47] Candelli M, Franza L, Pignataro G, Ojetti V, Covino M, et al. Interaction between Lipopolysaccharide and Gut Microbiota in Inflammatory Bowel Diseases. Int J Mol Sci 2021;22:6242
[48] Kelly JR, Kennedy PJ, Cryan JF, Dinan TG, Clarke G, et al.

Breaking down the barriers: the gut microbiome, intestinal permeability and stress-related psychiatric disorders. Front Cell Neurosci 2015;9:392.

[49] Santos-Marcos JA, Perez-Jimenez F, Camargo A. The role of diet and intestinal microbiota in the development of metabolic syndrome. J Nutr Biochem 2019;70:1-27.

[50] Singh AK, Vinayak M. Curcumin attenuates CFA induced thermal hyperalgesia by modulation of antioxidant enzymes and down regulation of TNF-α, IL-1β and IL-6. Neurochem Res 2015;40:463-472.

[51] Santos-Parker JR, Strahler TR, Bassett CJ, Bispham NZ, Chonchol MB, et al. Curcumin supplementation improves vascular endothelial function in healthy middle-aged and older adults by increasing nitric oxide bioavailability and reducing oxidative stress. Aging (Albany NY). 2017;9:187-208.

[52] Maiti P, Dunbar GL. Use of Curcumin, a Natural Polyphenol for Targeting Molecular Pathways in Treating Age-Related Neurodegenerative Diseases. Int J Mol Sci. 2018;19:1637.

[53] Yanaka A. Role of NRF2 in protection of the gastrointestinal tract against oxidative stress. J Clin Biochem Nutr 2018;63:18-25.

[54] Takahashi M, Suzuki K, Kim HK, Otsuka Y, Imaizumi A, et al. Effects of curcumin supplementation on exercise-induced oxidative stress in humans. Int J Sports Med 2014;35:469-475.

[55] Yuan F, Wu W, Ma L, Wang D, Hu M, et al. Turmeric and curcuminiods ameliorate disorders of glycometabolism among subjects with metabolic diseases: a systematic review and meta-analysis of randomized controlled trials. Pharmacol Res 2022;177:106121.

[56] Zhang HA, Kitts DDJM, Biochemistry C. Turmeric and its bioactive constituents trigger cell signaling mechanisms that protect against diabetes and cardiovascular diseases. Mol Cell Biochem 2021;476:3785-3814.

[57] Ashrafizadeh M, Ahmadi Z, Mohammadinejad R, Farkhondeh T, Samarghandian SJCMM. Curcumin activates the Nrf2 pathway and induces cellular protection against oxidative injury. Curr Mol Med 2020;20:116-133.

[58] Pivari F, Mingione A, Brasacchio C, Soldati LJN. Curcumin and type 2 diabetes mellitus: prevention and treatment. Nutrients 2019;11:1837.

[59] Sena-Júnior AS, Aidar FJ, Oliveira e Silva AMd, Estevam CdS, de Oliveira Carvalho CR, et al. Whether or not the effects of curcuma longa supplementation are associated with physical exercises in T1DM and T2DM: a systematic review. Nutrients 2020;13(1):124.

[60] Karłowicz-Bodalska K, Han S, Freier J, Smoleński M, Bodalska A. Curcuma longa as medicinal herb in the treatment of diabetic complications. Acta Pol Pharm 2017;74:605-610.

[61] Sousa DFd, Araújo MFMd, de Mello VD, Damasceno MMC, Freitas RWJFd. Cost-effectiveness of passion fruit albedo versus turmeric in the glycemic and lipaemic control of people with type 2 diabetes: Randomized clinical trial. J Am Coll Nutr 2021;40:679-688.

[62] Kurian GA, Manjusha V, Nair SS, Varghese T, Padikkala JJN. Short-term effect of G-400, polyherbal formulation in the management of hyperglycemia and hyperlipidemia conditions in patients with type 2 diabetes mellitus. Nutrition 2014;30:1158-1164.

[63] Neta JFdF, Veras VS, Sousa DFd, Cunha MdCdSO, Queiroz MVO, et al. Effectiveness of the piperine-supplemented Curcuma longa L. in metabolic control of patients with type 2 diabetes: a randomised double-blind placebo-controlled clinical trial. Int J Food Sci Nutr 2021;72:968-977.

[64] Cicero AFG, Fogacci F, Morbini M, Colletti A, Bove M, et al. Nutraceutical effects on glucose and lipid metabolism in patients with impaired fasting glucose: a pilot, double-blind, placebo-controlled, randomized clinical trial on a combined product. High Blood Press Cardiovasc Prev 2017;24:283-288.

[65] Uchio R, Muroyama K, Okuda-Hanafusa C, Kawasaki K, Yamamoto Y, et al. Hot water extract of Curcuma longa L. improves serum inflammatory markers and general health in subjects with overweight or prehypertension/mild hypertension: a randomized, double-blind, placebo-controlled trial. Nutrients 2019;11:1822.

[66] Tebboub I, Kechrid Z. Effect of curcuma on zinc, lipid profile and antioxidants levels in blood and tissue of streptozotocin-induced diabetic rats fed zinc deficiency diet. Arch Physiol Biochem 2021;127:162-169.

[67] Essa R, El Sadek AM, Baset ME, Rawash MA, Sami DG, et al. Effects of Turmeric (Curcuma longa) Extract in streptozocin-induced diabetic model. J Food Biochem 2019;43:e12988.

[68] El-Hadary A, Sitohy M. Safely effective hypoglycemic action of stevia and turmeric extracts on diabetic Albino rats. J Food Biochem 2021;45:e13549.

[69] Júnior ASS, Aidar FJ, Santos JLD, Estevam CDS, Dos Santos JDM, et al. Effects of resistance training and turmeric supplementation on reactive species marker stress in diabetic rats. 2020;12:1-12.

[70] Lai X, Tong D, Ai X, Wu J, Luo Y, et al. Amelioration of diabetic nephropathy in db/db mice treated with tibetan medicine formula Siwei Jianghuang Decoction Powder extract. Sci Rep 2018;8:1-11.

[71] Margină D, Olaru OT, Ilie M, Grădinaru D, Guțu C, et al. Assessment of the potential health benefits of certain total extracts from Vitis vinifera, Aesculus hyppocastanum and Curcuma longa. 2015;10:1681-1688.

[72] Dawane JS, Pandit VA, Bhosale MSK, Khatavkar PSJJoC, JCDR DR. Evaluation of effect of nishamalaki on STZ and HFHF diet induced diabetic neuropathy in wistar rats. 2016;10(10):FF01.

[73] Panda V, Deshmukh A, Singh S, Shah T, Hingorani L. An Ayurvedic formulation of Emblica officinalis and Curcuma longa alleviates insulin resistance in diabetic rats: Involvement of curcuminoids and polyphenolics. J Ayurveda Integr Med 2021;12:506-513.

[74] Rahman IU, Bashir M, Idrees M, Rahman KU, Khan MI. Benefits of Zubex beyond glycemic control: Evidence of the antiatherogenic effect. Chin J Integr Med 2016.

[75] Hussain N, Hashmi AS, Wasim M, Akhtar T, Saeed S, et al. Synergistic potential of Zingiber officinale and Curcuma longa to ameliorate diabetic-dyslipidemia. Pak J Pharm Sci 2018;31:491-498.

[76] Mustafa SB, Akram M, Asif HM, Qayyum I, Hashmi AM, et al. antihyperglycemic activity of hydroalcoholic extracts of selective medicinal plants Curcuma longa, Lavandula stoechas, Aegle marmelos, and Glycyrrhiza glabra and their polyherbal preparation in alloxan-induced diabetic mice. 2019;17:1559325819852503.

[77] Dosoky NS, Setzer WN. Chemical composition and biological activities of essential oils of Curcuma species. Nutrients 2018;10:1196.

[78] Zhao Y, Chen Z-Y. Roles of spicy foods and their bioac-

tive compounds in management of hypercholesterolemia. 2018;66:8662-8671.
[79] Amin F, Islam N, Anila N, Gilani AH. Clinical efficacy of the co-administration of Turmeric and Black seeds (Kalongi) in metabolic syndrome–A double blind randomized controlled trial–TAK-MetS trial. Complement Ther Med 2015;23:165-174.
[80] Adab Z, Eghtesadi S, Vafa MR, Heydari I, Shojaii A, et al. Effect of turmeric on glycemic status, lipid profile, hs-CRP, and total antioxidant capacity in hyperlipidemic type 2 diabetes mellitus patients. Phytother Res 2019;33:1173-1181.
[81] Dixit K, Kamath DV, Alluri KV, Davis B. Efficacy of a novel herbal formulation for weight loss demonstrated in a 16-week randomized, double-blind, placebo-controlled clinical trial with healthy overweight adults. Diabetes Obes Metab 2018;20:2633-2641.
[82] Ghaffari A, Rafraf M, Navekar R, Sepehri B, Asghari-Jafarabadi M, et al. Turmeric and chicory seed have beneficial effects on obesity markers and lipid profile in non-alcoholic fatty liver disease (NAFLD). Int J Vitam Nutr Res 2019;89:293-302.
[83] Patti AM, Al-Rasadi K, Katsiki N, Banerjee Y, Nikolic D, et al. Effect of a natural supplement containing curcuma longa, guggul, and chlorogenic acid in patients with metabolic syndrome. Angiology 2015;66:856-861.
[84] Turgut R, Kartal M, Akkol EK, Demirbolat İ, Taştan H. Development of cholesterol-lowering and detox formulations using bentonite and herbal ingredients. Front Pharmacol 2021;12:775789.
[85] Zhou S, Zhang Q, Gao Y, Liu F, Cao W, et al. Sargassum fusiforme together with turmeric extract and pomegranate peel extract alleviates obesity in high fat-fed C57BL/6J mice. Food Funct 2021;12:4654-4669.
[86] Leong XF. The spice for hypertension: Protective role of Curcuma longa. Biomed Pharmacol J 2018;11:1829-1840.
[87] Joshi P, Joshi S, Semwal DK, Verma K, Dwivedi J, et al. Role of curcumin in ameliorating hypertension and associated conditions: a mechanistic insight. Mol Cell Biochem 2022;477:2359-2385.
[88] Vafaeipour Z, Razavi BM, Hosseinzadeh H. Effects of turmeric (curcuma longa) and its constituent (curcumin) on the metabolic syndrome: An updated review. J Integr Med 2022;20:193-203.
[89] Hadi A, Pourmasoumi M, Ghaedi E, Sahebkar A. The effect of Curcumin/Turmeric on blood pressure modulation: A systematic review and meta-analysis. Pharmacol Res 2019;150:104505.
[90] Li KX, Wang ZC, Machuki JO, Li MZ, Wu YJ, et al. Benefits of curcumin in the vasculature: a therapeutic candidate for vascular remodeling in arterial hypertension and pulmonary arterial hypertension? Nutrients 2022;13:848867.
[91] Daryanti D, Pujiastuti RSE. The effect of nanoparticles turmeric consumption (curcuma domestica val) on blood pressure and lipid profile in hypertension patients with hypercholesterolemia. Int J Nurs Health Serv 2021;4:530-540.
[92] Bateni Z, Rahimi HR, Hedayati M, Afsharian S, Goudarzi R, et al. The effects of nano-curcumin supplementation on glycemic control, blood pressure, lipid profile, and insulin resistance in patients with the metabolic syndrome: A randomized, double-blind clinical trial. Phytother Res 2021;35:3945-3953.
[93] Lee S, Jo C, Choi HY, Lee K. Effect of co-administration of curcumin with amlodipine in hypertension. Nutrients 2021;13:2797.
[94] Srinivasan A, Selvarajan S, Kamalanathan S, Kadhiravan T, Prasanna Lakshmi NC, et al. Effect of Curcuma longa on vascular function in native Tamilians with type 2 diabetes mellitus: A randomized, double-blind, parallel arm, placebo-controlled trial. Phytother Res 2019;33:1898-1911.
[95] Khajehdehi P, Zanjaninejad B, Aflaki E, Nazarinia M, Azad F, et al. Oral supplementation of turmeric decreases proteinuria, hematuria, and systolic blood pressure in patients suffering from relapsing or refractory lupus nephritis: a randomized and placebo-controlled study. J Renal Nutr 2012;22:50-57.
[96] Kalhori A, Rafraf M, Navekar R, Ghaffari A, Jafarabadi MA. Effect of turmeric supplementation on blood pressure and serum levels of sirtuin 1 and adiponectin in patients with non-alcoholic fatty liver disease: a double-blind, randomized, placebo-controlled trial. Prevent Nutr Food Sci 2022;27:37-44.
[97] Nowak KL, Farmer-Bailey H, Wang W, You Z, Steele C. Curcumin Therapy to Treat Vascular Dysfunction in Children and Young Adults with ADPKD: A Randomized Controlled Trial. Clin J Am Soc Nephrol 2022;17:240-250.
[98] Zhuang XD, Liao LZ, Dong XB, Hu X, Guo Y, et al. Design, synthesis, and antihypertensive activity of curcumin-inspired compounds via ACE inhibition and vasodilation, along with a bioavailability study for possible benefit in cardiovascular diseases. Drug Des Devel Ther 2016;10:129-139.
[99] Kukongviriyapan U, Pannangpetch P, Kukongviriyapan V, Donpunha W, Sompamit K, et al. Curcumin protects against cadmium-induced vascular dysfunction, hypertension and tissue cadmium accumulation in mice. Nutrients 2014;6:1194-1208.
[100] Mulyani Y, Hasimun P, Sukmawati H. Effect of nori, a combination of turmeric (Curcuma longa) and gotu kola (Centella Asiatica) on blood pressure, modulation of ACE, eNOS and iNOS gene expression in hypertensive rats. Int J Res Pharm Sci 2021;12:2573-2581.
[101] Abd El-Hack ME, El-Saadony MT, Swelum AA, Arif M, Abo Ghanima MM, et al. Curcumin, the active substance of turmeric: its effects on health and ways to improve its bioavailability. J Sci Food Agric 2021;101:5747-5762.
[102] Zhang Y, Henning SM, Lee R-P, Huang J, Zerlin A, et al. Turmeric and black pepper spices decrease lipid peroxidation in meat patties during cooking. Int J Food Sci Nutr 2015;66:260-265.
[103] Komonsing N, Reyer S, Khuwijitjaru P, Mahayothee B, Müller J. Drying behavior and curcuminoids changes in turmeric slices during drying under simulated solar radiation as influenced by different transparent cover materials. Foods 2022;11:696.
[104] Pianpumepong P, Anal AK, Doungchawee G, Noomhorm A. Study on enhanced absorption of phenolic compounds of L actobacillus-fermented turmeric (C urcuma longa Linn.) beverages in rats. Int J Food Sci Technol 2012;47:2380-2387.
[105] Patil VM, Das S, Balasubramanian K. Quantum chemical and docking insights into bioavailability enhancement of curcumin by piperine in pepper. J Phys Chem A 2016;120:3643-3653.
[106] Prasad R, Shivay YS. Scientific and medical research support can increase export earnings from turmeric (curcuma longa). Natl Acad Sci Lett 2021;44:481-483.
[107] Hewlings S, Kalman D. Curcumin: A Review of Its Effects on Human Health. Foods (Basel, Switzerland). 2017.
[108] Kurien BT, Singh A, Matsumoto H, Scofield RH. Improving the solubility and pharmacological efficacy of curcumin by

heat treatment. Assay Drug Dev Techn 2007;5:567-576.
[109] Sharifi-Rad J, Rayess YE, Rizk AA, Sadaka C, Zgheib R, et al. Turmeric and its major compound curcumin on health: bioactive effects and safety profiles for food, pharmaceutical, biotechnological and medicinal applications. Front Pharmacol 2020;11:01021.
[110] Soleimani V, Sahebkar A, Hosseinzadeh H. Turmeric (Curcuma longa) and its major constituent (curcumin) as nontoxic and safe substances: Review. Phytother Res 2018;32:985-995.
[111] Fan X, Zhang C, Liu DB, Yan J, Liang HP. The clinical applications of curcumin: current state and the future. Curr Pharm Des 2013;19:2011-2031.
[112] Coelho MR, Romi MD, Ferreira D, Zaltman C. The use of curcumin as a complementary therapy in ulcerative colitis: a systematic review of randomized controlled clinical trials. Nutrients 2020;12:2296
[113] Wan Mohd Tajuddin WNB, Lajis NH, Abas F, Othman I, Naidu R. Mechanistic Understanding of Curcumin's Therapeutic Effects in Lung Cancer. Nutrients 2019;11:2989.
[114] Mishra S, Palanivelu K. The effect of curcumin (turmeric) on Alzheimer's disease: An overview. Ann Indian Acad Neurol 2008;11:13-19.
[115] White B, Judkins DZ. Does turmeric relieve inflammatory conditions? J Fam Pract 2011;3:155-156.
[116] Ahmad RS, Hussain MB, Sultan MT, Arshad MS, Waheed M, et al. Biochemistry, safety, pharmacological activities, and clinical applications of turmeric: a mechanistic review. Evid Based Complement Alternat Med 2020;2020:7656919.
[117] Balaji S, Chempakam B. Pharmacokinetics prediction and drugability assessment of diphenylheptanoids from turmeric (Curcuma longa L). Med Chem 2009;5:130-138.
[118] Naidu S, Suresh A. Effects of turmeric (Curcuma Longa) in dentistry. Int J Dev Res 2018;8:21828-21831.
[119] Timba PP, Giri SG, Panchal RV. Health benefits and possible risks of turmeric, garlic and ginger: a short review. Int Res J Eng Technol 2019;6:3.
[120] Hadi A, Pourmasoumi M, Ghaedi E, Sahebkar A. The effect of Curcumin/Turmeric on blood pressure modulation: A systematic review and meta-analysis. Pharmacol Res 2019;150:104505.
[121] Qin S, Huang L, Gong J, Shen S, Huang J, et al. Efficacy and safety of turmeric and curcumin in lowering blood lipid levels in patients with cardiovascular risk factors: a meta-analysis of randomized controlled trials. Nutrition J 2017;16:68.
[122] Srivastava A, Agarwal R, Chaturvedi TP, Chandra A, Singh OP. Clinical evaluation of the role of tulsi and turmeric in the management of oral submucous fibrosis: A pilot, prospective observational study. J Ayurveda Integr Med 2015;6:45-49.
[123] Vaughn AR, Branum A, Sivamani RK. Effects of Turmeric (Curcuma longa) on Skin Health: A Systematic Review of the Clinical Evidence. Phytother Res 2016;30:1243-1264.
[124] Yadav RP, Tarun G. Versatility of turmeric: A review the golden spice of life. J Pharmacogn Phytochem 2017;6:41-46.
[125] Bahadir Koca S, Ongun O, Ozmen O, Yigit NO. Subfertility effects of turmeric (Curcuma longa) on reproductive performance of Pseudotropheus acei. Anim Reprod Sci 2019;202:35-41.
[126] Ashfahani ED, Wiratmini NI, Sukmaningsih AASA. Motilitas dan viabilitas spermatozoa mencit (mus musculus l.) setelah pemberian ekstrak temu putih (curcuma zedoaria (berg.) roscoe.). Jurnal Biologi Udayana. 2010;14:20-23.
[127] Bhowmik D, Chiranjib, Kumar S. Turmeric: A Herbal and Traditional Medicine. Arch Appl Sci Res 2009;1:86-108.
[128] Unlu A, Nayir E, Dogukan Kalenderoglu M, Kirca O, Ozdogan M. Curcumin (Turmeric) and cancer. J BUON 2016;21:1050-1060.