Biomedical Effects of Turmeric

Subjects: Food Science & Technology | Integrative & Complementary Medicine | Nutrition & Dietetics
Contributor: Yamixa Delgado

Turmeric, also known as Curcuma longa, is a rhizomatous herbaceous perennial plant that belongs to the Zingiberaceae family (ginger family). This plant is highly branched with long aromatic leaves arranged in two rows and with flowers from white, green, yellowish, and purple-red colors.

Keywords: Phytonutrients ; Phytochemicals ; Turmeric ; Lipinski's rule of 5 ; Veber's rules ; Ghose filter ; Anticancer ; Antioxidant ; Antimicrobial ; Anti-inflammatory ; Immunomodulatory

1. Botanical Description

Curcuma plants are wildly cultivated in Southeast Asia and the Indian region, where various parts are used mainly for herbal medicinal applications, dietary supplements, and cuisine purposes [1][2]. An essential part of turmeric used as a spice and herbal supplement is the rhizome, which is adjacent to the plant's roots. Turmeric powder has a pungent taste and distinctive yellow/orange color due to pigments and curcuminoids phytochemicals in the rhizome [3]. Furthermore, primary metabolites (e.g., proteins and fats) and phytochemicals concentration dictate other physical properties and the color intensity of the turmeric powder, depending on factors such as the type of soil, crop fertilizers, and pH [4].

2. Phytochemicals

Turmeric's therapeutic properties may include a wide variety of conditions found in the literature, where most of them come from the bioactive compounds in its rhizome. For years, different research groups have shown that turmeric is extraordinarily rich in valuable phytochemicals with pharmacological properties including polyphenols (e.g., curcuminoids), terpenes (e.g., ar-, α- and β-turmerone, α-zingiber, and β-sesquiphellandrene), flavonoids, coumarins, saponins, tannins, and steroids [5][6][7]. The principal curcuminoids are curcumin and its derivatives demethoxycurcumin and bisdemethoxycurcumin [1][8][9]. Curcumin is considered the major bioactive phytochemicals from turmeric and is around 5% of the rhizome. Other bioactive compounds found in essential turmeric oils are aromatic-tumerones, α-santalene, and aromatic curcumene [10][11]. The biomedical uses of curcumin are limited by its short half-life, low stability, and limited bioavailability [12]. However, there are different strategies under investigation to overcome these limitations, such as using natural enhancers and developing delivery systems to encapsulate the curcumin [13][14]. Various studies have demonstrated that primary and secondary metabolites in turmeric extracts may enhance the bioavailability of curcumin in vivo [12][15]. Some other phytochemicals in combination with curcumin have shown synergistic effects increasing its bioavailability, e.g., quercetin, genistein, terpineol, epigallocatechin-3-gallate, and resveratrol [16][17].

3. Biomedical effects

3.1. Anticancer

Turmeric extracts and isolated curcumin have been extensively studied for cancer applications. Since 1985, turmeric extracts have demonstrated potent cytotoxic activity against cancer in vitro and in vivo studies [18]. Then, it also entered clinical studies for the treatment of cancer [19]. Curcumin has been shown to diminish tumor growth effectively, prevent tumor formation, angiogenesis, migration, and invasion by modulating several cell signaling pathways related to adhesion molecules, cell survival proteins, growth factors, transcription factors, cytokines, kinases, and receptors [20]. Different studies demonstrated that curcumin downregulates cyclin D1, cyclin E, and MDM2, and upregulates p21, p27, and p53 [21]. Due to the low bioavailability of pure curcumin, some researchers prefer to continue studies using turmeric extracts, co-administration with other phytochemicals, or the development of drug delivery systems. For example, Li et al. reported that turmeric extracts (200 mg/kg) induced in vivo tumor growth inhibition and anti-metastatic effects using colorectal CT26, HT29, and HCT116 cancer cells [22]. Furthermore, in combination with the phytochemical quercetin, it reveals a synergistic effect against lung, skin, colorectal, and breast cancer cells [23]. In addition, Almutairi et al. designed a model

that encapsulated curcumin in a chitosan polymer nanoparticle (115 nm) to increase its anticancer activity. This curcumin–chitosan nanoparticle showed a sensitive release in a more acidic pH environment, such as in cancer cells [24]. Moreover, several studies using curcumin as an anticancer agent include possible mechanisms of action [25][26][27][28][29].

3.2. Antioxidant

Curcumin is an extremely potent antioxidant by inhibiting the formation of reactive oxygen species [30]. In an in vitro study, Ak and Gülçin demonstrated the potent radical scavenging activity of curcumin by inhibiting >95% of lipid peroxidation [31]. Yuliani et al. investigated the antioxidant and neuroprotective effects of curcuminoids on neurons from Sprague–Dawley rats as a potential treatment for dementia. Turmeric extract (200 mg/kg) prevents spatial memory deficits, and its effects were comparable to the standard dementia medicine, citicoline [32]. In addition, Hossen et al. demonstrated the antioxidant properties and protective effects to hepatic organs in orally supplemented rats through a combination of curcumin (62%), flavonoids (37%), and ascorbic acid (10%). The possible mechanism of action was through antioxidant enzyme upregulation and lipid peroxidation inhibition, providing protective effects [33].

3.3. Antimicrobial

3.3.1. Antiviral

Several studies have demonstrated that the turmeric plant and the isolated phytochemical curcumin exhibited activity against a wide variety of viruses due to its potential to interfere with different cellular signaling pathways, inhibiting virus proliferation and viral expression [34]. The list of viruses that turmeric demonstrated activity are influenza A, dengue, viral hemorrhagic septicemia, human immunodeficiency, herpes simplex, Enterovirus 71, Zika, chikungunya, vesicular stomatitis, human respiratory syncytial, and others [35]. In general, curcumin strongly inhibits virus proliferation and expression. An in vitro study focused on the structure–activity relationship demonstrated that double bonds in the central carbon chain enhanced the curcumin activity against type A influenza virus by its interaction with the receptor-binding region [36]. On the other hand, in another study, researchers claimed that the hydroxyl groups and phenyl rings of curcumin are responsible for the antiviral effect against the herpes simplex virus [37]. Curcumin showed an excellent inhibitory effect in the micromolar range against transmissible gastroenteritis virus in cells in a dose-, temperature- and time-dependent manner [38]. In a very recent systematic review, Kunnumakkara et al. explained the potential of curcumin and other spices against SARS-COV-2 due to their anti-inflammatory properties to inhibit the cytokine storm [39]. Interestingly, curcumin has demonstrated antiviral activity against the SARS-CoV-2 by disrupting the binding of the spike protein to the ACE2 receptor and preventing the virus from entering cells. This group also found that curcumin positively regulates the action of the antioxidant molecule NRF2 while negatively regulating the master inflammatory molecule HMGB1 [40]. These findings suggest that turmeric and its main phytochemical curcumin could not only be a potential treatment but also a prevention alternative for viral infections.

3.3.2. Antibacterial

There are also reports showing the antibacterial activity of turmeric [6]. Bangun et al. developed an alginate-based drug delivery system of turmeric extract and tested its activity against *Staphylococcus aureus* (Gram-positive) and *Escherichia coli* (Gram-negative). The results showed that this turmeric drug delivery system affected both strains. However, there was more prominent growth inhibition on the Gram-positive bacteria than on the Gram-negative [41]. Another study performed by Czernicka, and colleagues elucidated the antimicrobial potential of turmeric extract against several Gram-positive strains (one strain of *Staphylococcus epidermidis* and two strains of *Bacillus subtilis*), revealing that the different fractions of this extract can inhibit bacterial growth [6]. In the same way, Shakeri et al. confirmed that Gram-positive bacteria are more sensitive to curcumin than Gram-negative bacteria due to their abundant hydrophilic lipopolysaccharide's outer membrane [42].

3.3.3. Antifungal

Another significant effect of turmeric is its antifungal activity. Chen et al. showed that turmeric extracts have potent antifungal activity against 20 pathogenic fungi (e.g., *Fusarium verticillioides*, *Curvularia pallescens*, *Colletotrichum falcatum*, *Aspergillus niger*, *Aspergillus terreus*, *Fusarium oxysporum*, *Fusarium moniliforme*, *Fusarium graminearum*, *Phoma wasabiae*, *Alternaria alternate*, *Botrytis cinerea*, *Chaetomium olivaceum*, *Penicillium pallidum*, *Mycogone perniciosa*, and *Verticillium dahlia*) by disrupting the synthesis of the main components of the fungal cell wall and interfering the protein synthesis. From this study, phytochemicals in turmeric have better antifungal activity working in combination than individual compounds [43]. Murugesh and colleagues elucidated that turmeric extracts exhibit a potent anticandidal effect against *Candida albicans* on in vitro studies [44]. In a randomized clinical trial, researchers demonstrated that the topical administration of curcumin 5% ointment could significantly reduce knee pain in osteoarthritis

patients [45]. This finding suggests considering turmeric topical use as a low-cost alternative with lesser side effects considering its antifungal capacity.

3.4. Anti-Inflammatory

Turmeric also exhibited potential to treat chronic pain and joint inflammation [46]. In a study using turmeric extracts combined with *Allium hookeri* extracts, researchers determined that this co-treatment restored the altered skin membrane and inhibited white blood cells and monocyte proliferation in inflamed skin models [47]. Bethapudi et al. demonstrated that oral administration of turmeric extract containing 57% of the bioactive turmerosaccharides significantly reduced pain and inflammation effects on an animal model (mimicking human osteoarthritis). This turmeric extract revealed a similar analgesic effect to tramadol on osteoarthritis pain [48]. In a recent study, Nicoliche et al. summarized the following curcumin's mechanisms of action against the inflammatory process: inhibition of NF-KB (nuclear factor kappa B), MMP-1, 3, 8, 9, and 13 (matrix metalloproteinases), nitric oxide synthase, MAPK (mitogen-activated protein kinase), MCP (monocyte chemoattractant protein), STAT (signal transduction and activation transcription), PI3K (phosphoinositide 3-kinase), lipo-oxygenase, JAK (Janus kinase), and COX-2 (cyclo-oxygenase-2), MIP (migration inhibitory protein); also inhibition on the expression of interleukin-1, -2, -6, -8, -12 and -1β, and TNF-α (tumor necrosis factor-α); significantly improve collagen repair [49]. The study also postulated that curcumin upregulates the peroxisome proliferator-activated receptor-γ (PPAR-γ) [50].

3.5. Immunomodulatory

As previously described here, turmeric has antioxidant, antimicrobial, and anti-inflammatory properties leading to improved immune response. In in vivo experiments to study graft-versus-host disease (induced after bone marrow transplantation), mice were pretreated with curcumin (100 µg/mouse). These curcumin-pretreated mice showed an increase in CD4+ and CD8+ cells before the transplant, preventing the disease [51]. Jian et al. studied the effects of curcumin as a dietary supplement in the male Hu sheep model, reporting changes in blood metabolites, antioxidant capacity, testicular development, and immune response. After four months of dietary supplementation, the sheep improved their reproductive system performance [52]. In vivo and clinical studies indicate that curcumin can positively affect several immune cells (i.e., T lymphocyte subsets, macrophages, dendritic cells, B lymphocytes, and natural killer cells), which diminishes the severity of different autoimmune diseases [53]. Additional studies found promising results in patients with several pro-inflammatory illnesses (i.e., cardiovascular disease, renal diseases, arthritis, Crohn's disease, ulcerative colitis, irritable bowel disease, pancreatitis, peptic ulcer, gastric ulcer, oral lichen planus, vitiligo, psoriasis, acute coronary syndrome, atherosclerosis, diabetes, lupus, acquired immunodeficiency syndrome, β-thalassemia, biliary dyskinesia, and Dejerine-Sottas disease) [54]. Most recently, a study showed that curcumin supports immunomodulatory responses by inhibiting the cell-mediated response of inflammatory cytokines and, thus, mitigating progression to pneumonia and acute respiratory distress syndrome (ARDS) after SARS-CoV-2 infection [40].

3.6. Predicted gastrointestinal (GI) absorption

The physicochemical properties for the main four most bioactive phytochemicals in turmeric (curcumin, demethoxycurcumin, bisdemethoxycurcumin and α-turmerone) were calculated based on the combination of Lipinski's, Ghose's, and Veber's rules (L-Ro5, GF, VR), summarized as follow: molecular weight (160-500 Da); hydrogen bond donors ≤5; hydrogen bond acceptors ≤10; molar refractivity (40-130); lipophilicity (-0.4–5.6); rotatable bonds ≤ 10: polar surface area <140; total number of atoms (20-70) [55],[56],[57],[58]. These are described as an approximation for the pharmacokinetics of a molecule in the body. From turmeric's phytochemicals, 100% (curcumin, demethoxycurcumin, bisdemethoxycurcumin and α-turmerone) comply with all of the "drug-likeness" rules. Accordingly, all these turmeric's phytochemicals are predicted to show high probability of absorption in the GI.

4. Contraindications

Despite the extensive evidence that reveals the beneficial effect of *Curcuma longa* extract, there might be several side effects and contraindications associated with its use. Previous studies reported that turmeric extract could increase bile secretion, triggering biliary colic and predisposing patients to have gallstones [59]. In addition, a high dose of turmeric supplementation in a 38-year-old man was related to inducing atrioventricular block, which disappeared once the supplementation was discontinued [60]. We must emphasize that this patient took 20–30 pills of curcumin supplement, 75 mg each, twice per day, when the physician's recommendation was to take only ten capsules per day, with at least four times being the recommended dosage. Furthermore, turmeric supplementation may increase the risk of bleeding in combination with anticoagulant drugs [61]. Moreover, turmeric extracts decreased insulin resistance in diabetic patients

due to their hypoglycemic effect [62]. Due to curcumin's iron chelating property, it is not recommended to patients with iron deficiency [63].

References

1. Chatzinasiou, L.; Booker, A.; MacLennan, E.; Mackonochie, M.; Heinrich, M. Turmeric (Curcuma longa L.) products: What quality differences exist? J. Herb. Med. 2019, 17-18, 100281.
2. Rao, P.S.; Ramanjaneyulu, Y.S.; Prisk, V.R.; Schurgers, L.J. A Combination of Tamarindus indica seeds and Curcuma longa Rhizome Extracts Improves Knee Joint Function and Alleviates Pain in Non-Arthritic Adults Following Physical Activity. Int. J. Med. Sci. 2019, 16, 845–853.
3. Hossain, M.A.; Ishimine, Y. Growth, yield and quality of turmeric (curcuma longa l.) cultivated on dark-red soil, gray soil and red soil in okinawa, japan. Plant Prod. Sci. 2005, 8, 482–486.
4. Dhakal, S.; Schmidt, W.F.; Kim, M.; Tang, X.; Peng, Y.; Chao, K. Detection of additives and chemical contaminants in turmeric powder using FT-IR spectroscopy. Foods 2019, 8, 143.
5. Amalraj, A.; Pius, A.; Gopi, S.; Gopi, S. Biological activities of curcuminoids, other biomolecules from turmeric and their de-rivatives—A review. J. Tradit. Complement. Med. 2016, 7, 205–233.
6. Czernicka, L.; Grzegorczyk, A.; Marzec, Z.; Antosiewicz, B.; Malm, A.; Kukula-Koch, W. Antimicrobial Potential of Single Metabolites of Curcuma longa Assessed in the Total Extract by Thin-Layer Chromatography-Based Bioautography and Image Analysis. Int. J. Mol. Sci. 2019, 20, 898.
7. Irshad, S.; Muazzam, A.; Shahid, Z.; Dalrymple, M.B. Curcuma longa (Turmeric): An auspicious spice for antibacterial, phytochemical and antioxidant activities. Pak. J. Pharm. Sci. 2018, 31, 2689–2696.
8. Choi, Y.; Ban, I.; Lee, H.; Baik, M.-Y.; Kim, W. Puffing as a Novel Process to Enhance the Antioxidant and Anti-Inflammatory Properties of Curcuma longa L. (Turmeric). Antioxidants 2019, 8, 506.
9. Rodríguez Castaño, P.; Parween, S.; Pandey, A.V. Bioactivity of curcumin on the cytochrome p450 enzymes of the steroido-genic pathway. Int. J. Mol. Sci. 2019, 20, 4606.
10. Toden, S.; Theiss, A.; Wang, X.; Goel, A. Essential turmeric oils enhance anti-inflammatory efficacy of curcumin in dextran sulfate sodium-induced colitis. Sci. Rep. 2017, 7, 1–12.
11. Yu, Y.; Shen, Q.; Lai, Y.; Park, S.Y.; Ou, X.; Lin, D.; Jin, M.; Zhang, W. Anti-inflammatory Effects of Curcumin in Microglial Cells. Front. Pharmacol. 2018, 9, 386.
12. Anand, P.; Kunnumakkara, A.B.; Newman, R.A.; Aggarwal, B.B. Bioavailability of Curcumin: Problems and Promises. Mol. Pharm. 2007, 4, 807–818.
13. Chen, Y.; Lu, Y.; Lee, R.J.; Xiang, G. Nano Encapsulated Curcumin: And Its Potential for Biomedical Applications. Int. J. Nanomed. 2020, ume 15, 3099–3120.
14. Agarwal, D.K.; Agarwal, S. Current Trends in Drug Delivery System of Curcumin and its Therapeutic Applications. Mini Rev. Med. Chem. 2020, 20, 1190–1232.
15. Kim, J.H.; Gupta, S.C.; Park, B.; Yadav, V.R.; Aggarwal, B.B. Turmeric (curcuma longa) inhibits inflammatory nuclear fac-tor (nf)-κb and nf-κb-regulated gene products and induces death receptors leading to suppressed proliferation, induced chemosensitization, and suppressed osteoclastogenesis. Mol. Nutr. Food Res. 2012, 56, 454–465.
16. Rizeq, B.; Gupta, I.; Ilesanmi, J.; Alsafran, M.; Rahman, M.; Ouhtit, A. The Power of Phytochemicals Combination in Cancer Chemoprevention. J. Cancer 2020, 11, 4521–4533.
17. Siviero, A.; Gallo, E.; Maggini, V.; Gori, L.; Mugelli, A.; Firenzuoli, F.; Vannacci, A. Curcumin, a golden spice with a low bio-availability. J. Herb. Med. 2015, 5, 57–70.
18. Kuttan, R.; Bhanumathy, P.; Nirmala, K.; George, M. Potential anticancer activity of turmeric (Curcuma longa). Cancer Lett. 1985, 29, 197–202.
19. Aggarwal, B.B.; Kumar, A.; Bharti, A.C. Anticancer potential of curcumin: Preclinical and clinical studies. Anticancer Res. 2003, 23, 363–398.
20. Kunnumakkara, A.B.; Bordoloi, D.; Harsha, C.; Banik, K.; Gupta, S.C.; Aggarwal, B.B. Curcumin mediates anticancer effects by modulating multiple cell signaling pathways. Clin. Sci. 2017, 131, 1781–1799.
21. Goel, A.; Kunnumakkara, A.B.; Aggarwal, B.B. Curcumin as "curecumin": From kitchen to clinic. Biochem. Pharm. 2008, 75, 787–809.

22. Li, M.; Yue, G.G.-L.; Tsui, S.K.-W.; Fung, K.-P.; Lau, C.B.-S. Turmeric extract, with absorbable curcumin, has potent anti-metastatic effect in vitro and in vivo. Phytomedicine 2018, 46, 131–141.

23. Srivastava, N.S.; Srivastava, R.A.K. Curcumin and quercetin synergistically inhibit cancer cell proliferation in multiple cancer cells and modulate Wnt/β-catenin signaling and apoptotic pathways in A375 cells. Phytomedicine 2019, 52, 117–128.

24. Almutairi, F.M.; el Rabey, H.A.; Tayel, A.A.; Alalawy, A.I.; Al-Duais, M.A.; Sakran, M.I.; Zidan, N.S. Augmented anti-cancer activity of curcumin loaded fungal chitosan nanoparticles. Int. J. Biol. Macromol. 2020, 155, 861–867.

25. Kasi, P.D.; Tamilselvam, R.; Skalicka-Woźniak, K.; Nabavi, S.M.; Daglia, M.; Bishayee, A.; Pazoki-Toroudi, H. Molecular targets of curcumin for cancer therapy: An updated review. Tumor Biol. 2016, 37, 13017–13028.

26. Liu, Y.; Sun, H.; Makabel, B.; Cui, Q.; Li, J.; Su, C.; Ashby, C.R., Jr.; Chen, Z.; Zhang, J. The targeting of non-coding RNAs by curcumin: Facts and hopes for cancer therapy (Review). Oncol. Rep. 2019, 42, 20–34.

27. Song, X.; Zhang, M.; Dai, E.; Luo, Y. Molecular targets of curcumin in breast cancer (Review). Mol. Med. Rep. 2019, 19, 23–29.

28. Wang, H.; Zhang, K.; Liu, J.; Yang, J.; Tian, Y.; Yang, C.; Li, Y.; Shao, M.; Su, W.; Song, N. Curcumin regulates cancer pro-gression: Focus on ncrnas and molecular signaling pathways. Front. Oncol. 2021, 11, 660712.

29. Wang, M.; Jiang, S.; Zhou, L.; Yu, F.; Ding, H.; Li, P.; Zhou, M.; Wang, K. Potential Mechanisms of Action of Curcumin for Cancer Prevention: Focus on Cellular Signaling Pathways and miRNAs. Int. J. Biol. Sci. 2019, 15, 1200–1214.

30. Tanvir, E.M.; Hossen, M.S.; Hossain, M.F.; Afroz, R.; Gan, S.H.; Khalil, M.I.; Karim, N. Antioxidant properties of popular turmeric (curcuma longa) varieties from bangladesh. J. Food Qual. 2017, 8471785.

31. Ak, T.; Gülçin, I. Antioxidant and radical scavenging properties of curcumin. Chem. Interact. 2008, 174, 27–37.

32. Yuliani, S.; Mustofa; Partadiredja, G. Turmeric (Curcuma longa L.) extract may prevent the deterioration of spatial memory and the deficit of estimated total number of hippocampal pyramidal cells of trimethyltin-exposed rats. Drug Chem. Toxicol. 2017, 41, 62–71.

33. Hossen, S.; Tanvir, E.M.; Prince, M.B.; Paul, S.; Saha, M.; Ali, Y.; Gan, S.H.; Khalil, I.; Karim, N. Protective mechanism of turmeric (Curcuma longa) on carbofuran-induced hematological and hepatic toxicities in a rat model. Pharm. Biol. 2017, 55, 1937–1945.

34. Praditya, D.; Kirchhoff, L.; Brüning, J.; Rachmawati, H.; Steinmann, J.; Steinmann, E. Anti-infective Properties of the Golden Spice Curcumin. Front. Microbiol. 2019, 10, 912.

35. Jennings, M.; Parks, R. Curcumin as an Antiviral Agent. Viruses 2020, 12, 1242.

36. Ou, J.L.; Mizushina, Y.; Wang, S.Y.; Chuang, D.Y.; Nadar, M.; Hsu, W.L. Structure-activity relationship analysis of curcumin analogues on anti-influenza virus activity. FEBS J. 2013, 280, 5829–5840.

37. Treml, J.; Gazdová, M.; Šmejkal, K.; Šudomová, M.; Kubatka, P.; Hassan, S.T.S. Natural Products-Derived Chemicals: Breaking Barriers to Novel Anti-HSV Drug Development. Viruses 2020, 12, 154.

38. Li, Y.; Wang, J.; Liu, Y.; Luo, X.; Lei, W.; Xie, L. Antiviral and virucidal effects of curcumin on transmissible gastroenteritis virus in vitro. J. Gen. Virol. 2020, 101, 1079–1084.

39. Kunnumakkara, A.B.; Rana, V.; Parama, D.; Banik, K.; Girisa, S.; Henamayee, S.; Thakur, K.K.; Dutta, U.; Garodia, P.; Gupta, S.C.; et al. COVID-19, cytokines, inflammation, and spices: How are they related? Life Sci. 2021, 119201.

40. Thimmulappa, R.K.; Mudnakudu-Nagaraju, K.K.; Shivamallu, C.; Subramaniam, K.J.T.; Radhakrishanan, A.; Bhojraj, S.; Kuppusamy, G. Antivarial and immunomodulatory activity of curcumin: A case for prophylatic therapy for COVID-19. Heliyon 2021, 7, e06350.

41. Bangun, H.; Arianto, A.; Bangun, Y.S.; Nainggolan, M. Antibacterial Activity of Mucoadhesive Gastroretentive Drug Delivery System of Alginate Beads Containing Turmeric Extract-PVP Solid Dispersion. Open Access Maced. J. Med. Sci. 2019, 7, 3868–3873.

42. Shakeri, A.; Panahi, Y.; Johnston, T.P.; Sahebkar, A. Biological properties of metal complexes of curcumin. BioFactors 2019, 45, 304–317.

43. Chen, C.; Long, L.; Zhang, F.; Chen, Q.; Chen, C.; Yu, X.; Liu, Q.; Bao, J.; Long, Z. Antifungal activity, main active compo-nents and mechanism of curcuma longa extract against fusarium graminearum. PLoS ONE 2018, 13, e0194284.

44. Murugesh, J.; Annigeri, R.G.; Mangala, G.K.; Mythily, P.H.; Chandrakala, J. Evaluation of the antifungal efficacy of differ-ent concentrations of curcuma longa on candida albicans: An in vitro study. JOMFP 2019, 23, 305.

45. Jamali, N.; Adib-Hajbaghery, M.; Soleimani, A. The effect of curcumin ointment on knee pain in older adults with osteoar-thritis: A randomized placebo trial. BMC Complement. Med. Ther. 2020, 20, 305.
46. Jurenka, J.S. Anti-inflammatory properties of curcumin, a major constituent of Curcuma longa: A review of preclinical and clinical research. Altern. Med. Rev. J. Clin. Ther. 2009, 14, 141–153.
47. Lee, S.-Y.; Cho, S.-S.; Li, Y.; Bae, C.-S.; Park, K.M.; Park, D.-H. Anti-inflammatory effect of curcuma longa and allium hook-eri co-treatment via nf-κb and cox-2 pathways. Sci. Rep. 2020, 10, 5718.
48. Velusami, C.C.; Bethapudi, B.; Murugan, S.; Illuri, R.; Mundkinajeddu, D. Bioactive turmerosaccharides from Curcuma longa Extract (NR-INF-02): Potential ameliorating effect on osteoarthritis pain. Pharmacogn. Mag. 2017, 13, 623–S627.
49. Nicoliche, T.; Maldonado, D.C.; Faber, J.; Silva, M.C.P. Evaluation of the articular cartilage in the knees of rats with induced arthritis treated with curcumin. PLoS ONE 2020, 15, e0230228.
50. Jacob, A.; Wu, R.; Zhou, M.; Wang, P. Mechanism of the Anti-inflammatory Effect of Curcumin: PPAR-γActivation. PPAR Res. 2007, 2007, 1–5.
51. Park, M.J.; Moon, S.J.; Lee, S.H.; Yang, E.J.; Min, J.K.; Cho, S.G.; Yang, C.W.; Park, S.H.; Kim, H.Y.; Cho, M.L. Curcumin attenuates acute graft-versus-host disease severity via in vivo regulations on th1, th17 and regulatory t cells. PLoS ONE 2013, 8, e67171.
52. Jiang, Z.; Wan, Y.; Li, P.; Xue, Y.; Cui, W.; Chen, Q.; Chen, J.; Wang, F.; Mao, D. Effect of Curcumin Supplement in Summer Diet on Blood Metabolites, Antioxidant Status, Immune Response, and Testicular Gene Expression in Hu Sheep. Animals 2019, 9, 720.
53. Abdollahi, E.; Momtazi, A.A.; Johnston, T.P.; Sahebkar, A. Therapeutic effects of curcumin in inflammatory and immune-mediated diseases: A nature-made jack-of-all-trades? J. Cell Physiol. 2018, 233, 830–848.
54. Gupta, S.C.; Patchva, S.; Aggarwal, B.B. Therapeutic Roles of Curcumin: Lessons Learned from Clinical Trials. AAPS J. 2013, 15, 195–218.
55. Asher, G.N.; Spelman, K. Clinical utility of curcumin extract. Altern. Ther. Health Med. 2013, 19, 20–22.
56. Lee, S.-W.; Nah, S.-S.; Byon, J.-S.; Ko, H.J.; Park, S.-H.; Lee, S.-J.; Shin, W.-Y.; Jin, D.-K. Transient complete atrioventricular block associated with curcumin intake. Int. J. Cardiol. 2011, 150, e50–e52.
57. Heck, A.M.; DeWitt, B.A.; Lukes, A.L. Potential interactions between alternative therapies and warfarin. Am. J. Health Pharm. 2000, 57, 1221–1227.
58. Pivari, F.; Mingione, A.; Brasacchio, C.; Soldati, L. Curcumin and Type 2 Diabetes Mellitus: Prevention and Treatment. Nutrients 2019, 11, 1837.
59. Jiao, Y.; Wilkinson, J.; Di, X.; Wang, W.; Hatcher, H.; Kock, N.D.; D'Agostino, R., Jr.; Knovich, M.A.; Torti, F.M.; Torti, S.V. Curcumin, a cancer chemopreventive and chemotherapeutic agent, is a biologically active iron chelator. Blood 2009, 113, 462–469.