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Therapeutic effects of turmeric in several diseases: An overview

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ABSTRACT

A nutraceutical product can be defined as a substance that has a physiological benefit or provides protection against chronic diseases. The term nutraceutical is a hybrid term derived from the union of "nutrition" and "pharmaceutical". The list of studied nutraceuticals is constantly changing and reflects ongoing market developments, research and consumer interest. Spices, in addition to giving color and taste to foods, are also important nutraceutical. Spices have been an integral part of human diets and commerce for millennia but recently, the recognition of the link between health and nutrition has strengthened their importance in the food sector and sparked the interest of researchers who increasingly engage in trying to determine the mechanisms of action of spices and the countless beneficial properties attributed to them. Among the many existing spices, turmeric is one of the most studied for its antioxidant, anti-inflammatory, antibacterial and anticancer properties. The purpose of this review is to briefly summarize the fundamental characteristics of turmeric and give an overview of the use of this spice in several diseases.

1. Introduction

The term "nutraceuticals" was invented by Stephen De Felice in 1989 from the union of "nutrition" and "pharmaceutical". According to De Felice, nutraceutical can be defined as, "a food (or part of a food) that provides medical or health benefits, including the prevention and/or treatment of a disease." [1]. Some of the most common methods for classifying nutraceuticals can be based on food sources, on the mechanism of action, on chemical nature. The food sources used as nutraceuticals are all natural and include dietary fiber, probiotics, polyunsaturated fatty acids, antioxidant vitamins and spices [2]. Several studies have shown the beneficial effects of nutraceuticals and their consumption can reduce diseases allowing humans to maintain an overall good health. Nutraceuticals have a significant role in the promotion of human health and disease prevention; they are a powerful instrument in promoting optimal health, longevity, and quality of life [3]. Most nutraceuticals have antioxidant activity, so they can contrast with conditions that imply the alteration of the redox state, such as diabetes, tumors and neurological disorders [4]. Several nutraceuticals also show promising results for the treatment of inflammatory bowel disease with minimal or no side effects [5].

2. Turmeric

Curcumin is a phenolic compound isolated as a yellow pigment from turmeric (common name of Curcuma longa). Turmeric is an Indian spice derived from the rhizome of the plant, perennial member of the Zingiberaceae family, cultivated in India and other parts of Southeast Asia [6]. The phenolic compounds are natural phytochemicals derived mainly from phenylalanine and less frequently from tyrosine and are widely present in food and nutraceuticals. Recently it has been shown that phenolic compounds have an inhibitory effect on cancer and its ability to metastasize (C. Y [7]. and, precisely because of the potential protective effects against oxidative damage, these compounds, including curcumin and its derivatives, are capturing the attention of the scientific world. The medicinal properties of turmeric have been known for thousands of years but the exact mechanisms of action and active components have only recently been analyzed. It has been traditionally used in Asian countries as a medical herb for its antioxidant, anti-inflammatory, anti-migraine, antimicrobial and anti-tumor properties, but it is recognized and used all over the world in many different ways because of its multiple potentialities. For example, in India the turmeric containing curcumin is used in the curry, in Japan it is served in tea, in

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Thailand it is part of the composition of cosmetics, in China it is used as a dye, in Malaysia as an antiseptic, in Pakistan as an anti-inflammatory agent, in the United States it is found in mustard sauce, cheese, butter and fries, as a preservative and colorant. Curcumin is available in various formulations: capsules, tablets, ointments, energy drinks, soaps and cosmetics [8].

2.1. Components of turmeric

Turmeric consists of a group of three curcuminoids: curcumin (77%), demetossicurcumin (17%) and bisdemetossicurcumina (3%), as well as volatile oils such as tumerone, atlantone and zingiberone, sugars, proteins and resins. Curcuminoids have been recognized by the US Food and Drug Administration (FDA) as safe and tolerable substances, even at doses of between 4 and 8 mg per day [9]. Curcumin is the main component of turmeric, it is also known as diferuloylmethane and is a yellow-orange crystalline solid. The molecule consists of two 4-hydroxy-3-methoxy-phenyl bound to a α, β-diketon unsaturated carbon bridge acting as a Michael acceptor. Curcumin displays a keto–enol tautomerism with the keto and enol forms existing in given proportions; when dissolved, the enol form predominates. Curcumin is a relatively unstable compound that degrades quickly from neutral to alkaline solutions [10].

3. Properties of curcumin

Among the several natural remedies studied today, curcumin has interested researchers for its profound medicinal values [11]. This compound has shown a great variety of biological functions, such as antibacterial, anti-inflammatory, antimicrobial, and anti-cancer effects (Fig. 1) [12]. Scientific research has confirmed the numerous pharmacological effects of curcumin and established its ability to act as a potential therapeutic agent against several chronic diseases [13].

3.1. Curcumin as a chelating agent

Curcumin is able to chelate metals thanks to the presence in its structure of the β-diketone function (C [14]. The metal ions are required by the body for many important functions and their plasma concentration must remain within the physiological limits, otherwise there will be some deficiency or excess. Chelation therapy is used in cases in which it is necessary to reduce the levels of a metal inside the body or increase them in case of deficiency [15]. The chelator can also be used as a scavenger, able to bind potentially toxic metals, neutralize them and eliminate them from the body, or for its ability to selectively transport the metal into the cell nucleus, allowing it to bind DNA, thus inhibiting the proliferation of cancer cells.

3.2. Curcumin in neurological diseases

Neurological disorders are different pathologies of the central and peripheral nervous system. These disorders produce epilepsy, Alzheimer disease (AD), Parkinson's disease (PD), migraine, brain tumors and traumatic disorders of the nervous system. Several studies conducted on different cell types from the nervous system (such as neurons, astrocytes and microglia) have demonstrated the neuroprotective properties of turmeric [16–18]. The ability of turmeric to prevent the development of neurodegenerative diseases such as AD and PD is specifically due to its anti-inflammatory and antioxidant properties.

The development of AD is mainly attributed to environmental factors, in particular: diet, smoking, cardiovascular diseases, type 2 diabetes and serious cranio-cerebral injuries. The dominant theory of the AD development is amyloid cascade hypothesis, but at the same time, in the etiology of this disease it is important the overphosphorylation of

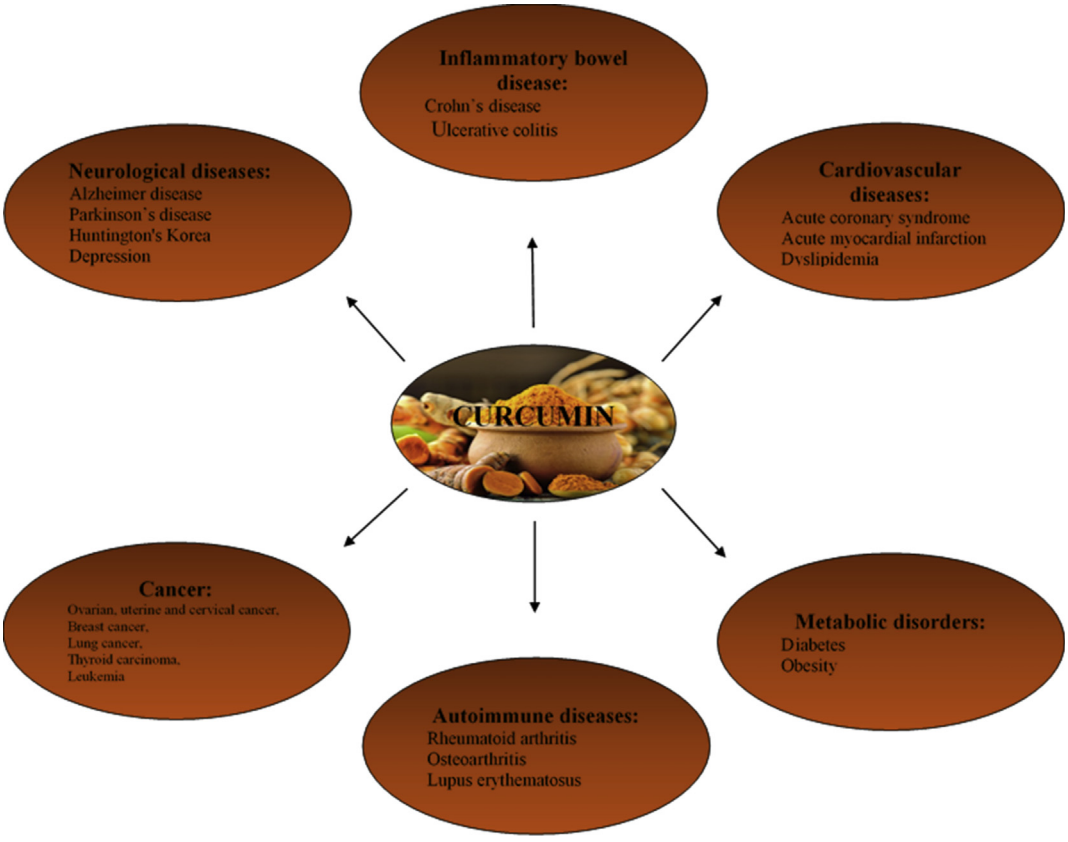

Fig. 1. Turmeric has beneficial effects in several diseases such as neurological disorders, inflammatory bowel diseases, cardiovascular diseases, metabolic disorders, autoimmune diseases and different types of cancer.

tau protein [19]. In vitro studies have shown that curcumin can bind Aβ, thus influencing the peptide aggregation and inhibiting fibrils formation and elongation [20]. Moreover, curcumin can enhance Aβ cellular uptake (L. [21], avoiding plaques deposition and preventing cellular insults induced by the peptide (H [22]. In vivo experiments have allowed to demonstrate that curcumin is able to rescue the distorted neuritic morphology near Aβ plaques [23], to decrease Aβ serum level (Y. J [24]. and to attenuate inflammation and microglia activation in AD mouse models. Furthermore, curcumin can modulate tau protein processing and phosphorylation [25].

Parkinson's disease is characterized by the abnormal accumulation and aggregation of the pre-synaptic protein α-synuclein in the dopaminergic neurons as Lewy bodies (LBs). Curcumin was found to directly modulate the aggregation of α-synuclein in vitro as well as in in vivo studies [26]. Oral and intravenous administration of curcumin was able to modulate dopaminergic damage suppressing apoptosis, inducing microglial activation and improving the locomotion [27].

Moreover, other studies described a powerful capacity of curcumin to decrease Huntington protein aggregation [28] ameliorating disease symptoms by suppressing cell death [29].

Depression is another neurological disorder for which the beneficial effects of turmeric have been demonstrated; it was observed that treatment with curcumin altered the biomarkers of depression and improved the mood of the patients [30,31]. Several studies have been conducted in this regard and have shown that turmeric is a safe and effective compound for the treatment of patients with depressive disorder [32] and that treatment with turmeric has been effective in improving several related symptoms in the mood in these patients [30].

3.3. Curcumin in inflammatory bowel diseases

Inflammatory bowel disease (IBD) is a type of chronic and relapsing disorder characterized by inflammation of the gastrointestinal tract [33]. Crohn's disease (CD) and ulcerative colitis (UC) are the two primary forms of inflammatory bowel disease. CD can affect any part of the gastrointestinal tract and affects the entire bowel wall. Several studies have suggested that Escherichia coli (AIEC) strains with invasive adhesion play an important role in CD; two AIEC strains, LF82 and 083:H1, have been shown to increase the expression of pro-inflammatory cytokines and some mucosal immune markers in CD colon biopsies [34]. UC is restricted to the colon and the rectum and disease is confined to the intestinal epithelium. Because of its anti-inflammatory properties, it was decided to conduct studies to determine the effects of turmeric in these diseases. Studies have shown that curcumin has potential to improve Crohn's inflammatory disease [35] and causes greater improvements in disease activity in patients with UC [36]. The anti-inflammatory properties and beneficial effects of curcumin have also been demonstrated for other gastrointestinal conditions, including dyspepsia, Helicobacter pylori infection, peptic ulcer and irritable bowel syndrome [6,37].

3.4. Curcumin for cardiovascular diseases

The effect of curcumin has been tested in patients with cardiovascular diseases such as acute coronary syndrome, acute myocardial infarction and dyslipidemia. Curcumin inhibits oxidative stress, apoptosis and inflammation and exerts cardioprotective effects. Besides curcumin can be beneficial for lipoprotein metabolism because it is involved in the reduction of low-density lipoprotein cholesterol and triglycerides, and augmentation of high-density lipoprotein [38]. In a study on the effectiveness of curcumin on cardiovascular risk factors in individuals with coronary artery disease, it has been determined that serum triglyceride, LDL and VLDL cholesterol levels decrease considerably in the group of individuals taking curcumin [39]. An even more recent study has shown that curcumin could be used as a safe and well tolerated adjunct to statins to control hyperlipidemia [40].

3.5. Curcumin and metabolic disorders

Among metabolic disorders, diabetes and obesity are certainly the most widespread. These diseases are closely associated with high calorie and/or poor-quality diets and sedentary lifestyles [41]. In addition, low grade chronic inflammation is associated with obesity and contributes to insulin resistance and the development of diabetes [42]. Curcumin plays a role in diabetes management; its positive effects occur by reducing insulin resistance and hyperlipidemia. Curcumin down-regulates the differentiation of pre-adipocytes to adipocytes, up-regulates adipocyte energy metabolism, induces apoptosis, and suppresses angiogenesis in adipose tissue. Curcumin administration has been shown to result in the reduction of leptin, resistin, and visfatin, while simultaneously increasing the expression of adiponectin [43].

3.6. Curcumin in autoimmune diseases

Several studies have demonstrated that curcumin inhibits inflammation in many autoimmune and inflammatory diseases such as atherosclerosis, arthritis, experimental autoimmune neuritis and encephalomyelitis ([44].

In Rheumatoid Arthritis (RA) curcumin was found to decrease the expression of pro-inflammatory cytokines (such as IL-1β), chemokine (such as MCP-1), and growth-related oncogene/keratinocyte chemoattractant (GRO/KC); curcumin can also decrease the gene expression of adhesion molecules, β3 and β7 integrins, and thereby decrease joint inflammation in RA [45].

Curcumin has been known to exert anti-inflammatory effects on osteoarthritis through the inhibition of NF-κB and the suppression of important regulators of inflammation such as TNF- α, IL-1β, IL-6, MCP-1, prostaglandin E2, cyclooxygenase-II, activator protein-1, as well as JNK, MAPK, and PI3K/Akt pathways [46].

The administration of curcumin appears beneficial for the treatment of systemic lupus erythematosus, an inflammatory and chronic autoimmune-mediated disease recognized by the accumulation of autoantibodies and immune complexes in distinct organs, elevation of autoreactive and inflammatory T cells, along with inappropriate rise of plasma proinflammatory cytokines. Actually, curcumin can afford to recover an imbalance present among T-helper cell subsets, regulatory T cells, and dendritic cells observed in these patients [47].

3.7. Curcumin and AIDS

Because of its antioxidant, anti-inflammatory, anticancer, antiviral and antibacterial nature, curcumin can be used for the treatment of HIV-AIDS. The human immunodeficiency virus (HIV), a lentivirus, belongs to the subgroup of retrovirus and causes destruction of the immune cells. The most advanced stage of HIV infection is Acquired Immunodeficiency Syndrome (AIDS) [48]. Nowadays there is no definitive cure for HIV infection; however antiretroviral (ARV) drugs are being used to control the viral transmission. In a 2015 study the effectiveness of curcumin in multiple steps of HIV infection and multiplication has been demonstrated [49]. Furthermore, in patients with HIV, treatment with turmeric represents a promising strategy to minimize side effects of antiretroviral therapy (ART) [33,50]; V. [51]; V [52,53]. by improving lipid profile and insulin sensitivity [54].

3.8. Curcumin and its application in cancer

Cancer is one of the most common causes of death globally. Treatment of cancer varies and typically involves surgery, radiotherapy and chemotherapy. The use of natural products in cancer therapy is an active area of research and curcumin is one of the most studied natural products due to its numerous health benefits and pharmacological effects including antiproliferation, apoptosis induction, antiangiogenesis, anti-inflammatory and antioxidant activities. In vitro studies showed a

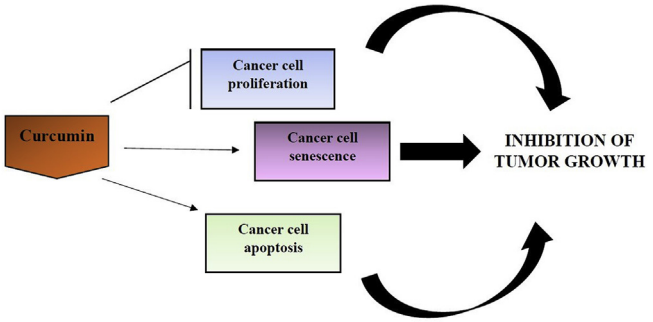

Fig. 2. Mechanism of action of turmeric on cancer cells: turmeric inhibits the growth of tumors by blocking proliferation and inducing the senescence and apoptosis of cancer cells.

remarkable ability of curcumin to suppress cancer cell growth and proliferation in several different cancer cell lines, inducing apoptosis by inhibiting or downregulating intracellular transcription factors (Fig. 2). These factors include NF-κB, activator protein1 (AP-1), cyclooxygenase II (COX-2), nitric oxide synthase, matrix metalloproteinase-9 (MMP-9), and STAT3 [55].

Several studies have shown the antitumor effects of turmeric against ovarian cancer [56], uterine cancer [57,58] and cervical cancer [59]; B [60,61]. Curcumin has shown a strong ability to counter prostate cancer both in vitro and in vivo. In a 2017 study, Liu and his collaborators treated with curcumin two prostate cancer cell lines (Du145 and 22RV1). Results were inhibition of in vitro proliferation and invasion, and cell cycle arrest [62]. Another study revealed that curcumin induced an Endoplasmic Reticulum stress-mediated apoptosis in PC3 and promoted cell death in these cells associated with cell cycle arrest, increased reactive oxygen species, autophagy [63].

Curcumin has been reported to suppress the STAT3 phosphorylation in small cell lung cancer (SCLC); this results in inhibition of proliferation, cell cycle, migration, invasion and angiogenesis of SCLC cells [64]. More recent research has shown that turmeric exhibits cytotoxicity even against non-small-cell lung cancer (NSCLC) by reducing mitochondrial transmembrane potential and inducing ROS production (C [65]. Through the inhibition of STAT3, curcumin also induces cell cycle arrest of different lines of esophageal squamous cell carcinoma (ESCC) [62].

Curcumin significantly inhibits the proliferation of various breast cancer cell lines, such as T47D, MCF7, MDA-MB-231 and MDA-MB-468 [66] and might be a promising agent for preventing breast cancer by attenuating formation and virulence of breast cancer stem cells (BCSCs), primarily responsible for tumor relapse, treatment-resistance and metastasis [67].

Curcumin showed the ability to reduce the survival of several cell lines of thyroid carcinoma. It inhibits invasion and migration of FTC 133 cells via down-regulation of PI3K/Akt signaling pathway and inhibition of MMP-1, MMP-7 and cyclooxygenase-2 (COX-2) [68], suppresses multiple metastatic steps of BCPAP cells including attachment and migration (L. [69], induces apoptosis of TPC1 cells through the modulation of antiapoptotic and proapoptotic factors and proteins involved in cell cycle regulation [70], reduces in vitro aggressiveness in SW1736 and 8505C cell lines [71].

Recently, anticancer effects of turmeric have been demonstrated on different types of leukemia, alone and in combination with chemotherapy agents [72]. Curcumin and its metabolite, tetrahydro curcumin, have potential applications in the treatment of acute myeloid leukemia by inducing cell death through the apoptosis pathway and via an autophagy pathway, respectively [73].

4. Curcumin bioavailability

The bioavailability of curcumin has been studied extensively in the last three decades. Several studies have shown that curcumin is poorly absorbed, rapidly metabolized and rapidly excreted; therefore, it has a limited systemic bioavailability [74]. This is because curcumin is a poorly water-soluble drug (about 11 ng/mL) and susceptible to degradation, particularly under alkaline conditions (L [75]. When curcumin is orally ingested, the major portion is excreted through the feces and only small portion is absorbed within the intestine. The liver is the main organ responsible for the metabolism of curcumin; the absorbed curcumin suffers a rapid metabolism in the liver and plasma. Despite its innumerable beneficial effects, curcumin has little therapeutic use due to its poor bioavailability. The useful pharmacological properties but poor bioavailability of curcumin have stimulated development of technologies to improve oral delivery of the compound [76]. Among the different strategies adopted to increase the bioavailability of curcumin there is the use of adjuvants, nanoparticles, liposomes, micelles and phospholipid complexes. The adjuvants were selected for their ability to prevent the rapid metabolism of curcumin, interfering with the enzymes that catalyze the metabolism of this molecule. Among the adjuvants, a widely studied substance is piperine, a constituent of Piper nigrum and Piper longum, which is able to increase the bioavailability of curcumin by 20 times. Several studies have shown that the combined use of turmeric and pepper enhances the effect of curcumin (T [77–81].

5. Conclusions

To date there are numerous studies conducted on nutraceuticals and spices, because these substances have sparked the interest of researchers for their many beneficial properties. Turmeric is considered an important nutraceutical due to its several properties, its beneficial effects on health and its safety. As reported in this review, a large number of studies have been conducted to investigate the effects of curcumin, the main constituent of turmeric, in various diseases such as neurological, inflammatory bowel, cardiovascular and autoimmune diseases, metabolic disorders and several types of cancer. Despite its countless beneficial properties, curcumin has a great limitation: it has a poor bioavailability because of its poor water solubility. More recent researches aim to find strategies to increase oral delivery of this compound; in this way the effects of turmeric can be further enhanced.

Declaration of interests

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

References

[1] E.K. Kalra, Nutraceutical–definition and introduction, AAPS PharmSci 5 (3) (2003), https://doi.org/10.1208/ps050325 E25-E25.
[2] R. Verma, M. Pandey, S. Saraf, Nutraceuticals: New Era of Medicine and Health 3 (2010).
[3] B. Chauhan, G. Kumar, N. Kalam, S.H. Ansari, Current concepts and prospects of herbal nutraceutical: a review, "J. Adv. Pharm. Technol. Research"" (JAPTR)" 4 (1) (2013) 4–8, https://doi.org/10.4103/2231-4040.107494.
[4] H. Nasri, A. Baradaran, H. Shirzad, M. Rafieian-Kopaei, New concepts in nutraceuticals as alternative for pharmaceuticals, Int. J. Prev. Med. 5 (12) (2014) 1487–1499.
[5] A.M. Parian, B.N. Limketkai, N.D. Shah, G.E. Mullin, Nutraceutical supplements for inflammatory bowel disease, Nutr. Clin. Pract. 30 (4) (2015) 551–558, https://doi.org/10.1177/0884533615586598.
[6] J.S. Jurenka, Anti-inflammatory properties of curcumin, a major constituent of Curcuma longa: a review of preclinical and clinical research, Altern. Med. Rev. 14 (2) (2009) 141–153.
[7] C.Y. Zhang, L. Zhang, H.X. Yu, J.D. Bao, R.R. Lu, Curcumin inhibits the metastasis of K1 papillary thyroid cancer cells via modulating E-cadherin and matrix metalloproteinase-9 expression, Biotechnol. Lett. 35 (7) (2013) 995–1000, https://doi.org/10.1007/s10529-013-1173-y.

[8] S.C. Gupta, G. Kismali, B.B. Aggarwal, Curcumin, a component of turmeric: from farm to pharmacy, Biofactors 39 (1) (2013) 2–13, https://doi.org/10.1002/biof.1079.

[9] S.J. Hewlings, D.S. Kalman, Curcumin: a review of its' effects on human health, Foods 6 (10) (2017), https://doi.org/10.3390/foods6100092.

[10] J. Zhu, K.Z. Sanidad, E. Sukamtoh, G. Zhang, Potential roles of chemical degradation in the biological activities of curcumin, Food Funct 8 (3) (2017) 907–914, https://doi.org/10.1039/c6fo01770c.

[11] S. Prasad, S.C. Gupta, A.K. Tyagi, B.B. Aggarwal, Curcumin, a component of golden spice: from bedside to bench and back, Biotechnol. Adv. 32 (6) (2014) 1053–1064, https://doi.org/10.1016/j.biotechadv.2014.04.004.

[12] A.B. Kunnumakkara, D. Bordoloi, G. Padmavathi, J. Monisha, N.K. Roy, S. Prasad, B.B. Aggarwal, Curcumin, the golden nutraceutical: multitargeting for multiple chronic diseases, Br. J. Pharmacol. 174 (11) (2017) 1325–1348, https://doi.org/10.1111/bph.13621.

[13] G. Grynkiewicz, P. Slifirski, Curcumin and curcuminoids in quest for medicinal status, Acta Biochim. Pol. 59 (2) (2012) 201–212.

[14] C. Zhang, A. Browne, D. Child, R.E. Tanzi, Curcumin decreases amyloid-beta peptide levels by attenuating the maturation of amyloid-beta precursor protein, J. Biol. Chem. 285 (37) (2010) 28472–28480, https://doi.org/10.1074/jbc.M110.133520.

[15] S. Srichairatanakool, C. Thephinlap, C. Phisalaphong, J.B. Porter, S. Fucharoen, Curcumin contributes to in vitro removal of non-transferrin bound iron by deferiprone and desferrioxamine in thalassemic plasma, Med. Chem. 3 (5) (2007) 469–474.

[16] M. Karlstetter, E. Lippe, Y. Walczak, C. Moehle, A. Aslanidis, M. Mirza, T. Langmann, Curcumin is a potent modulator of microglial gene expression and migration, J. Neuroinflammation 8 (2011) 125, https://doi.org/10.1186/1742-2094-8-125.

[17] S. Lavoie, Y. Chen, T.P. Dalton, R. Gysin, M. Cuenod, P. Steullet, K.Q. Do, Curcumin, quercetin, and tBHQ modulate glutathione levels in astrocytes and neurons: importance of the glutamate cysteine ligase modifier subunit, J. Neurochem. 108 (6) (2009) 1410–1422, https://doi.org/10.1111/j.1471-4159.2009.05908.x.

[18] A.M. Santos, T. Lopes, M. Oleastro, I.V. Gato, P. Floch, L. Benejat, ... A.S. Guerreiro, Curcumin inhibits gastric inflammation induced by Helicobacter pylori infection in a mouse model, Nutrients 7 (1) (2015) 306–320, https://doi.org/10.3390/nu7010306.

[19] P. Tecza, L. Zylinska, [Preventive effects of curcumin and resveratrol in Alzheimer's disease], Przegl. Lek. 73 (5) (2016) 320–323.

[20] K. Ono, K. Hasegawa, H. Naiki, M. Yamada, Curcumin has potent anti-amyloidogenic effects for Alzheimer's beta-amyloid fibrils in vitro, J. Neurosci. Res. 75 (6) (2004) 742–750, https://doi.org/10.1002/jnr.20025.

[21] L. Zhang, M. Fiala, J. Cashman, J. Sayre, A. Espinosa, M. Mahanian, ... M. Rosenthal, Curcuminoids enhance amyloid-beta uptake by macrophages of Alzheimer's disease patients, J. Alzheimer's Dis. 10 (1) (2006) 1–7.

[22] H. Kim, B.S. Park, K.G. Lee, C.Y. Choi, S.S. Jang, Y.H. Kim, S.E. Lee, Effects of naturally occurring compounds on fibril formation and oxidative stress of beta-amyloid, J. Agric. Food Chem. 53 (22) (2005) 8537–8541, https://doi.org/10.1021/jf051985c.

[23] M. Garcia-Alloza, L.A. Borrelli, A. Rozkalne, B.T. Hyman, B.J. Bacskai, Curcumin labels amyloid pathology in vivo, disrupts existing plaques, and partially restores distorted neurites in an Alzheimer mouse model, J. Neurochem. 102 (4) (2007) 1095–1104, https://doi.org/10.1111/j.1471-4159.2007.04613.x.

[24] Y.J. Wang, P. Thomas, J.H. Zhong, F.F. Bi, S. Kosaraju, A. Pollard, ... X.F. Zhou, Consumption of grape seed extract prevents amyloid-beta deposition and attenuates inflammation in brain of an Alzheimer's disease mouse, Neurotox. Res. 15 (1) (2009) 3–14, https://doi.org/10.1007/s12640-009-9000-x.

[25] M. Tang, C. Taghibiglou, The mechanisms of action of curcumin in alzheimer's disease, J. Alzheimer's Dis. 58 (4) (2017) 1003–1016, https://doi.org/10.3233/jad-170188.

[26] N. Sharma, B. Nehru, Curcumin affords neuroprotection and inhibits alpha-synuclein aggregation in lipopolysaccharide-induced Parkinson's disease model, Inflammopharmacology 26 (2) (2018) 349–360, https://doi.org/10.1007/s10787-017-0402-8.

[27] W. Tripanichkul, E.O. Jaroensuppaperch, Curcumin protects nigrostriatal dopaminergic neurons and reduces glial activation in 6-hydroxydopamine hemiparkinsonian mice model, Int. J. Neurosci. 122 (5) (2012) 263–270, https://doi.org/10.3109/00207454.2011.648760.

[28] M.A. Hickey, C. Zhu, V. Medvedeva, R.P. Lerner, S. Patassini, N.R. Franich, ... M.F. Chesselet, Improvement of neuropathology and transcriptional deficits in CAG 140 knock-in mice supports a beneficial effect of dietary curcumin in Huntington's disease, Mol. Neurodegener. 7 (2012) 12, https://doi.org/10.1186/1750-1326-7-12.

[29] A. Chongtham, N. Agrawal, Curcumin modulates cell death and is protective in Huntington's disease model, Sci. Rep. 6 (2016) 18736, https://doi.org/10.1038/srep18736.

[30] A.L. Lopresti, M. Maes, G.L. Maker, S.D. Hood, P.D. Drummond, Curcumin for the treatment of major depression: a randomised, double-blind, placebo controlled study, J. Affect. Disord. 167 (2014) 368–375, https://doi.org/10.1016/j.jad.2014.06.001.

[31] A.L. Lopresti, M. Maes, M.J. Meddens, G.L. Maker, E. Arnoldussen, P.D. Drummond, Curcumin and major depression: a randomised, double-blind, placebo-controlled trial investigating the potential of peripheral biomarkers to predict treatment response and antidepressant mechanisms of change, Eur. Neuropsychopharmacol. 25 (1) (2015) 38–50, https://doi.org/10.1016/j.euroneuro.2014.11.015.

[32] J. Sanmukhani, V. Satodia, J. Trivedi, T. Patel, D. Tiwari, B. Panchal, ... C.B. Tripathi, Efficacy and safety of curcumin in major depressive disorder: a randomized controlled trial, Phytother Res. 28 (4) (2014) 579–585, https://doi.org/10.1002/ptr.5025.

[33] M. Aguas, J. Del Hoyo, R. Faubel, P. Nos, Use of telemedicine in inflammatory bowel disease: a real monitoring option? Expert Rev. Gastroenterol. Hepatol. 10 (8) (2016) 879–881, https://doi.org/10.1080/17474124.2016.1200464.

[34] G. Mazzarella, A. Perna, A. Marano, A. Lucariello, V. Rotondi Aufiero, A. Sorrentino, ... A. De Luca, Pathogenic role of associated adherent-invasive Escherichia coli in Crohn's disease, J. Cell. Physiol. 232 (10) (2017) 2860–2868, https://doi.org/10.1002/jcp.25717.

[35] P.R. Holt, S. Katz, R. Kirshoff, Curcumin therapy in inflammatory bowel disease: a pilot study, Dig. Dis. Sci. 50 (11) (2005) 2191–2193, https://doi.org/10.1007/s10620-005-3032-8.

[36] V. Singla, V. Pratap Mouli, S.K. Garg, T. Rai, B.N. Choudhury, P. Verma, ... V. Ahuja, Induction with NCB-02 (curcumin) enema for mild-to-moderate distal ulcerative colitis - a randomized, placebo-controlled, pilot study, J Crohns Colitis 8 (3) (2014) 208–214, https://doi.org/10.1016/j.crohns.2013.08.006.

[37] L. Manente, A. Lucariello, C. Costanzo, R. Viglietti, G. Parrella, R. Parrella, ... V. Esposito, Suppression of pre adipocyte differentiation and promotion of adipocyte death by anti-HIV drugs, In Vivo 26 (2) (2012) 287–291.

[38] S. Ganjali, G.M. Dallinga-Thie, L.E. Simental-Mendia, M. Banach, M. Pirro, A. Sahebkar, HDL functionality in type 1 diabetes, Atherosclerosis 267 (2017) 99–109, https://doi.org/10.1016/j.atherosclerosis.2017.10.018.

[39] P. Mirzabeigi, A.H. Mohammadpour, M. Salarifar, K. Gholami, M. Mojtahedzadeh, M.R. Javadi, The effect of curcumin on some of traditional and non-traditional cardiovascular risk factors: a pilot randomized, double-blind, placebo-controlled trial, Iran. J. Pharm. Res. (IJPR) 14 (2) (2015) 479–486.

[40] Y. Panahi, P. Kianpour, R. Mohtashami, S.S. Soflaei, A. Sahebkar, Efficacy of phospholipidated curcumin in nonalcoholic fatty liver disease: a clinical study, J. Asian Nat. Prod. Res. (2018) 1–8, https://doi.org/10.1080/10286020.2018.1505873.

[41] J.C. Han, D.A. Lawlor, S.Y.S. Kimm, Childhood obesity, Lancet (London, England) 375 (9727) (2010) 1737–1748, https://doi.org/10.1016/S0140-6736(10)60171-7.

[42] G.S. Hotamisligil, Inflammation, metaflammation and immunometabolic disorders, Nature 542 (2017) 177, https://doi.org/10.1038/nature21363 https://www.nature.com/articles/nature21363#supplementary-information.

[43] J. Hajavi, A.A. Momtazi, T.P. Johnston, M. Banach, M. Majeed, A. Sahebkar, Curcumin: a naturally occurring modulator of adipokines in diabetes, J. Cell. Biochem. 118 (12) (2017) 4170–4182, https://doi.org/10.1002/jcb.26121.

[44] A. Shehzad, G. Rehman, Y.S. Lee, Curcumin in inflammatory diseases, Biofactors 39 (1) (2013) 69–77, https://doi.org/10.1002/biof.1066.

[45] J.L. Funk, J.N. Oyarzo, J.B. Frye, G. Chen, R.C. Lantz, S.D. Jolad, ... B.N. Timmermann, Turmeric extracts containing curcuminoids prevent experimental rheumatoid arthritis, J. Nat. Prod. 69 (3) (2006) 351–355, https://doi.org/10.1021/np050327j.

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

[47] A.A. Momtazi-Borojeni, S.M. Haftcheshmeh, S.A. Esmaeili, T.P. Johnston, E. Abdollahi, A. Sahebkar, Curcumin: a natural modulator of immune cells in systemic lupus erythematosus, Autoimmun. Rev. 17 (2) (2018) 125–135, https://doi.org/10.1016/j.autrev.2017.11.016.

[48] R.M. Granich, C.F. Gilks, C. Dye, K.M. De Cock, B.G. Williams, Universal voluntary HIV testing with immediate antiretroviral therapy as a strategy for elimination of HIV transmission: a mathematical model, Lancet 373 (9657) (2009) 48–57, https://doi.org/10.1016/s0140-6736(08)61697-9.

[49] S. Prasad, A.K. Tyagi, Curcumin and its analogues: a potential natural compound against HIV infection and AIDS, Food Funct 6 (11) (2015) 3412–3419, https://doi.org/10.1039/c5fo00485c.

[50] N. Coppola, A. Perna, A. Lucariello, S. Martini, M. Macera, M.A. Carleo, ... A. De Luca, Effects of treatment with Maraviroc a CCR5 inhibitor on a human hepatic stellate cell line, J. Cell. Physiol. 233 (8) (2018) 6224–6231, https://doi.org/10.1002/jcp.26485.

[51] V. Esposito, L. Manente, A. Lucariello, A. Perna, R. Viglietti, M. Gargiulo, ... A. Chirianni, Role of FAP48 in HIV-associated lipodystrophy, J. Cell. Biochem. 113 (11) (2012) 3446–3454, https://doi.org/10.1002/jcb.24221.

[52] V. Esposito, A. Perna, A. Lucariello, M.A. Carleo, R. Viglietti, V. Sangiovanni, ... A. Chirianni, Different impact of antiretroviral drugs on bone differentiation in an in vitro model, J. Cell. Biochem. 116 (10) (2015) 2188–2194, https://doi.org/10.1002/jcb.25169.

[53] A. Perna, A. Lucariello, C. Sellitto, I. Agliata, M.A. Carleo, V. Sangiovanni, A. De Luca, Different cell cycle modulation in SKOV-3 ovarian cancer cell line by anti-HIV drugs, Oncol. Res. 25 (9) (2017) 1617–1624, https://doi.org/10.3727/096504017x14905635363102.

[54] L.T. da Silva, B.T. Santillo, A. de Almeida, A. Duarte, T.M. Oshiro, Using dendritic cell-based immunotherapy to treat HIV: how can this strategy be improved? Front. Immunol. 9 (2018) 2993, https://doi.org/10.3389/fimmu.2018.02993.

[55] W.H. Lee, C.Y. Loo, P.M. Young, D. Traini, R.S. Mason, R. Rohanizadeh, Recent advances in curcumin nanoformulation for cancer therapy, Expert Opin. Drug Deliv. 11 (8) (2014) 1183–1201, https://doi.org/10.1517/17425247.2014.916686.

[56] M. Saydmohammed, D. Joseph, V. Syed, Curcumin suppresses constitutive activation of STAT-3 by up-regulating protein inhibitor of activated STAT-3 (PIAS-3) in ovarian and endometrial cancer cells, J. Cell. Biochem. 110 (2) (2010) 447–456, https://doi.org/10.1002/jcb.22558.

[57] A. Kondo, T. Takeda, B. Li, K. Tsuiji, M. Kitamura, T.F. Wong, N. Yaegashi, Epigallocatechin-3-gallate potentiates curcumin's ability to suppress uterine

leiomyosarcoma cell growth and induce apoptosis, Int. J. Clin. Oncol. 18 (3) (2013) 380–388, https://doi.org/10.1007/s10147-012-0387-7.
[58] X. Li, W. Xie, C. Xie, C. Huang, J. Zhu, Z. Liang, ... C. Zhong, Curcumin modulates miR-19/PTEN/AKT/p53 axis to suppress bisphenol A-induced MCF-7 breast cancer cell proliferation, Phytother Res. 28 (10) (2014) 1553–1560, https://doi.org/10.1002/ptr.5167.
[59] Y.P. Dang, X.Y. Yuan, R. Tian, D.G. Li, W. Liu, Curcumin improves the paclitaxel-induced apoptosis of HPV-positive human cervical cancer cells via the NF-kappaB-p53-caspase-3 pathway, Exp Ther Med 9 (4) (2015) 1470–1476, https://doi.org/10.3892/etm.2015.2240.
[60] B. Kim, H.S. Kim, E.J. Jung, J.Y. Lee, K.T. B, J.M. Lim, Y.S. Song, Curcumin induces ER stress-mediated apoptosis through selective generation of reactive oxygen species in cervical cancer cells, Mol. Carcinog. 55 (5) (2016) 918–928, https://doi.org/10.1002/mc.22332.
[61] P.C. Thacker, D. Karunagaran, Curcumin and emodin down-regulate TGF-beta signaling pathway in human cervical cancer cells, PLoS One 10 (3) (2015) e0120045, , https://doi.org/10.1371/journal.pone.0120045.
[62] T. Liu, H. Chi, J. Chen, C. Chen, Y. Huang, H. Xi, ... Y. Si, Curcumin suppresses proliferation and in vitro invasion of human prostate cancer stem cells by ceRNA effect of miR-145 and lncRNA-ROR, Gene 631 (2017) 29–38, https://doi.org/10.1016/j.gene.2017.08.008.
[63] M. Rivera, Y. Ramos, M. Rodriguez-Valentin, S. Lopez-Acevedo, L.A. Cubano, J. Zou, ... N.M. Boukli, Targeting multiple pro-apoptotic signaling pathways with curcumin in prostate cancer cells, PLoS One 12 (6) (2017) e0179587, , https://doi.org/10.1371/journal.pone.0179587.
[64] S.F. Peng, C.Y. Lee, M.J. Hour, S.C. Tsai, D.H. Kuo, F.A. Chen, ... J.S. Yang, Curcumin-loaded nanoparticles enhance apoptotic cell death of U2OS human osteosarcoma cells through the Akt-Bad signaling pathway, Int. J. Oncol. 44 (1) (2014) 238–246, https://doi.org/10.3892/ijo.2013.2175.
[65] C. Wang, X. Song, M. Shang, W. Zou, M. Zhang, H. Wei, H. Shao, Curcumin exerts cytotoxicity dependent on reactive oxygen species accumulation in non-small-cell lung cancer cells, Future Oncol. 15 (11) (2019) 1243–1253, https://doi.org/10.2217/fon-2018-0708.
[66] S. Hu, Y. Xu, L. Meng, L. Huang, H. Sun, Curcumin inhibits proliferation and promotes apoptosis of breast cancer cells, Exp Ther Med 16 (2) (2018) 1266–1272, https://doi.org/10.3892/etm.2018.6345.
[67] H.F. Gu, X.Y. Mao, M. Du, Prevention of breast cancer by dietary polyphenols-role of cancer stem cells, Crit. Rev. Food Sci. Nutr. (2019) 1–16, https://doi.org/10.1080/10408398.2018.1551778.
[68] X. Xu, J. Qin, W. Liu, Curcumin inhibits the invasion of thyroid cancer cells via down-regulation of PI3K/Akt signaling pathway, Gene 546 (2) (2014) 226–232, https://doi.org/10.1016/j.gene.2014.06.006.
[69] L. Zhang, X. Cheng, Y. Gao, C. Zhang, J. Bao, H. Guan, ... Y. Sun, Curcumin inhibits metastasis in human papillary thyroid carcinoma BCPAP cells via down-regulation of the TGF-beta/Smad2/3 signaling pathway, Exp. Cell Res. 341 (2) (2016) 157–165, https://doi.org/10.1016/j.yexcr.2016.01.006.
[70] A. Perna, A. De Luca, L. Adelfi, T. Pasquale, B. Varriale, T. Esposito, Effects of different extracts of curcumin on TPC1 papillary thyroid cancer cell line, BMC Complement Altern. Med. 18 (1) (2018) 63, https://doi.org/10.1186/s12906-018-2125-9.
[71] L. Allegri, F. Rosignolo, C. Mio, S. Filetti, F. Baldan, G. Damante, Effects of nutraceuticals on anaplastic thyroid cancer cells, J. Cancer Res. Clin. Oncol. 144 (2) (2018) 285–294, https://doi.org/10.1007/s00432-017-2555-7.
[72] H. Kouhpeikar, A.E. Butler, F. Bamian, G.E. Barreto, M. Majeed, A. Sahebkar, Curcumin as a therapeutic agent in leukemia, J. Cell. Physiol. 234 (8) (2019) 12404–12414, https://doi.org/10.1002/jcp.28072.
[73] Y.H. Tseng, S.S. Chiou, J.P. Weng, P.C. Lin, Curcumin and tetrahydrocurcumin induce cell death in Ara-C-resistant acute myeloid leukemia, Phytother Res. 33 (4) (2019) 1199–1207, https://doi.org/10.1002/ptr.6316.
[74] S.K. Vareed, M. Kakarala, M.T. Ruffin, J.A. Crowell, D.P. Normolle, Z. Djuric, D.E. Brenner, Pharmacokinetics of curcumin conjugate metabolites in healthy human subjects, Cancer Epidemiol. Biomark. Prev. 17 (6) (2008) 1411–1417, https://doi.org/10.1158/1055-9965.epi-07-2693.
[75] L. Zhang, W. Zhu, C. Yang, H. Guo, A. Yu, J. Ji, ... G. Zhai, A novel folate-modified self-microemulsifying drug delivery system of curcumin for colon targeting, Int. J. Nanomed. 7 (2012) 151–162, https://doi.org/10.2147/ijn.s27639.
[76] P. Ratnatilaka Na Bhuket, A. El-Magboub, I.S. Haworth, P. Rojsitthisak, Enhancement of curcumin bioavailability via the prodrug approach: challenges and prospects, Eur. J. Drug Metab. Pharmacokinet. 42 (3) (2017) 341–353, https://doi.org/10.1007/s13318-016-0377-7.
[77] T. Esposito, A. Lucariello, E. Hay, M. Contieri, P. Tammaro, B. Varriale, ... A. Perna, Effects of curcumin and its adjuvant on TPC1 thyroid cell line, Chem. Biol. Interact. 305 (2019) 112–118, https://doi.org/10.1016/j.cbi.2019.03.031.
[78] A. Jangra, M. Kwatra, T. Singh, R. Pant, P. Kushwah, Y. Sharma, ... B.K. Bezbaruah, Piperine augments the protective effect of curcumin against lipopolysaccharide-induced neurobehavioral and neurochemical deficits in mice, Inflammation 39 (3) (2016) 1025–1038, https://doi.org/10.1007/s10753-016-0332-4.
[79] G. Kaur, M. Invally, M. Chintamaneni, Influence of piperine and quercetin on antidiabetic potential of curcumin, J. Complement. Integr. Med. 13 (3) (2016) 247–255, https://doi.org/10.1515/jcim-2016-0016.
[80] V.M. Patil, S. Das, K. Balasubramanian, Quantum chemical and docking insights into bioavailability enhancement of curcumin by piperine in pepper, J. Phys. Chem. A 120 (20) (2016) 3643–3653, https://doi.org/10.1021/acs.jpca.6b01434.
[81] S. Singh, P. Kumar, Neuroprotective potential of curcumin in combination with piperine against 6-hydroxy dopamine induced motor deficit and neurochemical alterations in rats, Inflammopharmacology 25 (1) (2017) 69–79, https://doi.org/10.1007/s10787-016-0297-9.