Journal of Medical Sciences at NEOMED
Volume 2, Issue 1, January 2024

TURMERIC - The Golden Herb!

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ABSTRACT

The curry spice, turmeric, is used to provide color and flavor to food, as well as for its health benefits. Turmeric contains many polyphenolic compounds known as curcuminoids, with curcumin being the most prominent curcuminoid. In this perspective, the health benefits of turmeric curcuminoids are highlighted. Specifically, this perspective summarizes the source, history, and the general use of turmeric. The pharmacology, especially the antioxidative and anti-inflammatory properties, safety, and the pharmacokinetic profile, as well as the therapeutic potential of curcuminoids in several disease conditions is discussed. The development of semi-synthetic forms and novel formulations for delivery of curcuminoids is mentioned. This article reflects upon the current status of turmeric use and the potential challenges, as well as future steps needed for development of curcuminoids as therapeutic agents in the clinic.

Keywords: curcumin, inflammation, oxidative stress, polyphenols, turmeric

INTRODUCTION

Herbs have been used over many millennia as spices - providing flavor, color, and preservation to food along with health benefits.[1] Of particular interest is turmeric, which in recent years has gained immense popularity for its potential health benefits.[2] This perspective provides a succinct overview of turmeric. A general background of the turmeric herb, such as its source, history, geographical distribution, and general use is reviewed. The article discusses the curcuminoids present in turmeric and their pharmacodynamic and pharmacokinetic characteristics, along with their therapeutic potential in several illnesses. The bioavailability, safety, semi-synthetic forms, and novel dosage forms incorporating curcuminoids are highlighted. Also discussed are the potential challenges and future directions for the effective development of turmeric compounds as mainstream therapeutic agents for clinical use.

CURCUMINOIDS

The curry spice, turmeric, also called "Indian saffron," is obtained from the underground rhizomes of the plant Curcuma longa, which belongs to the ginger family, Zingiberaceae. The rhizomes are boiled, dried, and ground to produce an intense yellow powder. The turmeric plant is native to the tropical parts of South Asia and Southeast Asia and is extensively used in the cuisine of these regions to impart color and flavor.[3]

Turmeric has been used for thousands of years in many traditional systems of alternative medicine such as Ayurveda, Siddha, and Unani from South Asia, as well as traditional Chinese medicine.[4] Within those cultures, turmeric can be recommended for several illnesses such as indigestion, infections, arthritis, rheumatism, and respiratory ailments.[4-7] Anecdotally, turmeric is credited with cardioprotective, neuroprotective, anticarcinogenic, and lipid-lowering properties.[8,9] Efforts need to be made to make the general public aware of the potential health benefits and therapeutic applications of turmeric. Turmeric powder contains polyphenolic compounds known as curcuminoids which impart a deep yellow color. Commercially available turmeric powder contains approximately 77% curcumin (curcumin I), the principal curcuminoid, along with 18% desmethoxycurcumin (curcumin II), and 5% bisdemethoxycurcumin (curcumin III)[3] (Figure 1). Semi-synthetic curcuminoids such as diacetyl-curcumin, hexahydrocurcumin, isoxazole-curcumin, and hydrazinocurcumin, along with metal complexes of curcumin have been synthesized and evaluated for their biological effects.[9-11] The curcumin structure has also been utilized as a scaffold in drug-discovery programs.[12,13] Utilization of curcuminoids, both naturally occurring as well as semi-synthetic forms, in the drug discovery process needs more rigor and effort especially in the publication and dissemination of scientific literature.

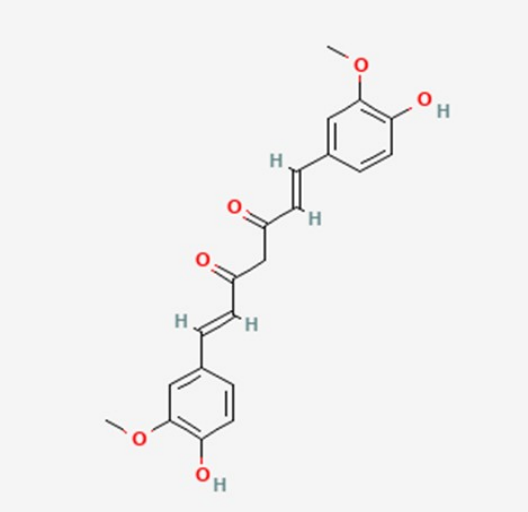

Figure 1A. Structure of

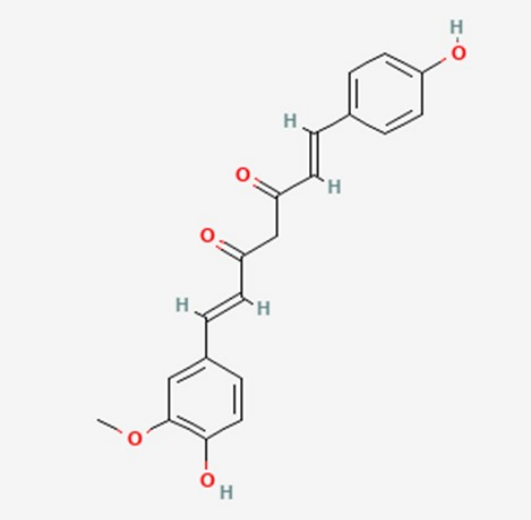

Figure 1B. Structure of demethoxycurcumin[15]

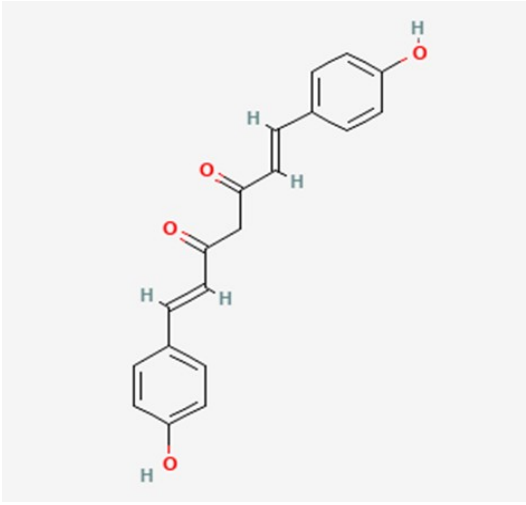

Figure 1C. Structure of bisdemethoxycurcumin[16]

PHARMACODYNAMICS AND THERAPEUTICS

In the past three decades, considerable amount of research has been conducted to investigate the biological, pharmacological, and therapeutic effects of curcumin.[17-20] Curcumin's therapeutic potential in autoimmune, cardiovascular, neoplastic, and neuro-degenerative diseases is vastly due to its robust antioxidative and anti-inflammatory properties, as well as its ability to modulate a wide array of signaling mechanisms.[21] Dietary polyphenols, such as antho-cyanins from berries, catechins and theaflavins from green and black tea respectively, resveratrol from grapes, wine, and peanuts, as well as curcuminoids from turmeric, have all been shown to possess potent antioxidative and anti-inflammatory effects.[22,23] Polyphenolic phytomolecules possess multiple hydroxyl groups, phenolic groups, and conjugated double bonds which contribute to their free radical quenching properties.[24] Polyphenols, such as curcumin, consumed as part of diet or taken as supplements, attenuate the oxidative stress and inflammation produced due to harmful stimuli, ionizing radiation, environmental pollutants, and pathophysiological factors thus providing both prophylactic and therapeutic benefits. Curcumin has been shown to produce robust antioxidative effects and its effects on multiple markers of oxidative stress, including antioxidant enzymes, has been well documented.[25,26] The anti-inflammatory effects of dietary polyphenols, along with their suppressive effects on inflammatory pathways, has been well characterized.[23,27] The past two decades have seen significant research in elucidating the anti-inflammatory portfolio of curcumin. Curcumin's inhibitory effects on a range of inflammatory cytokines such as interleukins, chemokines, and cachectin (tumor necrosis factor-α, TNF-α) has been systematically examined by several researchers.[28-32] Nuclear factor-κβ (NF-κβ) is known as the master switch of the inflammatory cascade and is the most prominent transcription factor responsible for activating inflammatory pathways. The Aggarwal laboratory demonstrated for the first time the curcumin-mediated suppression of NF-κβ and its related target genes.[31] Curcumin has been shown to modulate an amazing array of molecular targets such as growth factors, transcription factors, enzymes such as kinases, inflammatory cytokines, adhesion molecules, and apoptotic proteins.[32]

MOLECULAR EFFECTS OF CURCUMIN

Curcuminoids have been extensively investigated in both *in vitro* and *in vivo* pre-clinical models, as well as in clinical studies of chronic disorders such as autoimmune (e.g., rheumatoid arthritis, ulcerative colitis), anti-infective, cardio-vascular, neoplastic (e.g., colon cancer, pancreatic cancer, head and neck cancers, melanoma), and neurodegenerative diseases (e.g., Alzheimer's disease,

Parkinson's disease).[26,33-36] Curcuminoids have demonstrated their suppressive effects on markers of oxidative stress, inflammation, and pathogenesis in the aforementioned studies. Since oxidative stress and inflammation are ubiquitous in the pathophysiology of disease, the antioxidative and anti-inflammatory effects of curcumin, along with its pleiotropic effects on a multitude of biochemical pathways and molecular targets ultimately contribute to its prophylactic and therapeutic potential in the wide range of diseases. Curcumin has been shown to affect inflammatory cytokines, antioxidant enzymes, regulatory proteins, signaling molecules, and cell proliferation in a multitude of pathophysiological states (Figure 2).[37-39]

Similar to other dietary polyphenols, curcuminoids in combination have demonstrated considerable synergy, as compared to curcumin alone, in their antioxidative, anti-inflammatory, and therapeutic potential, as well as their bioavailability.[40] The National Toxicology Program (NTP) evaluated the potential toxicity and carcinogenicity of turmeric oleoresin containing about 80% curcumin. The NTP and subsequent studies did not find any evidence for carcinogenic potential.[41-44] Although both rats and mice fed with curcumin for two years at the highest dose (50,000 ppm) showed a higher incidence of ulcers, hyperplasia, and hyperkeratosis of the forestomach, the NTP report suggested that turmeric has minimal potential for toxicity at clinical doses.[41] Curcumin at a low dose of 2000 ppm also did not alter the life span of genetically heterogenous mice.[45] While there is considerable progress in the pre-clinical dose-ranging and safety studies of turmeric curcuminoids, dosing and safety studies in humans is considerably lacking and needs further investigation. It is important that the efficacy and safety be examined in humans. Thus, clinical investigation of the therapeutic benefits and potential adverse effects of curcumin is much needed.

PHARMACOKINETIC PROFILE AND DOSAGE FORMS OF CURCUMIN

The pharmacokinetic profile of curcumin has been well studied and documented.[46,47] Curcumin is poorly absorbed and undergoes extensive metabolism resulting in low bioavailability. Curcumin is relatively unstable in aqueous media and forms degradation products such as ferulic acid and vanillin, as well as reduction products such as tetrahydrocurcumin and hexahydrocurcumin. Curcumin undergoes extensive conjugation metabolism in the liver to form glucuronide and sulfate conjugates (Figure 3).[47,48] The biological activity of curcumin degradation products and metabolites has been studied by several researchers. Both degradation products such as ferulic acid and vanillin, as well as reduction products such as tetrahydrocurcumin and hexahydrocurcumin, showed pharmacological effects similar to curcumin. The biological activity of curcumin glucuronide and sulfate conjugates, which are highly hydrophilic, is not well studied.[45,47,48]

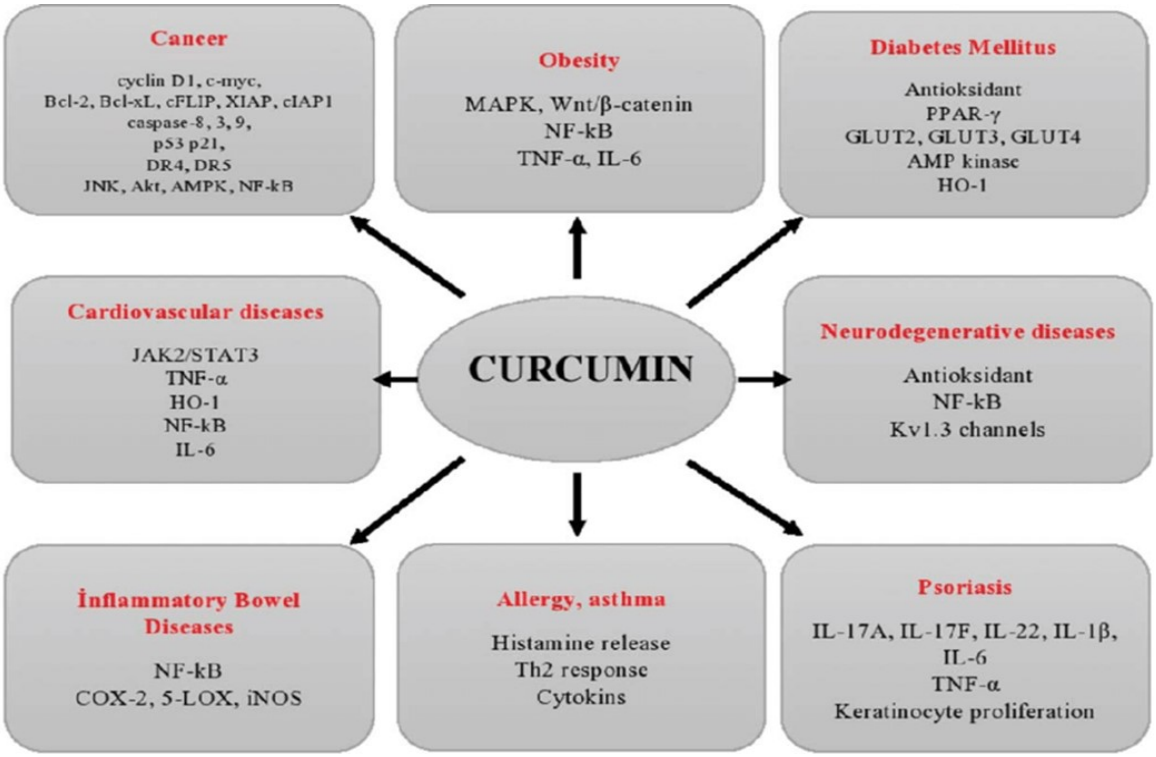

Figure 2. Molecular therapeutic targets of curcumin[2]

Low bioavailability of naturally occurring polyphenolic compounds, such as curcumin, resveratrol, and tea polyphenols, has been the primary hurdle in the therapeutic development and translational pharmacotherapy of these agents.[46,47] Considerable efforts have been made to enhance the clinical bioavailability of curcumin, such as the use of novel drug delivery systems and other agents such as piperine and lecithin.[46,47] Curcumin's ability to cross the blood brain barrier has also been examined, since it is a critical aspect of its neurotherapeutic potential. Curcumin has been shown to cross the blood brain barrier after oral, intramuscular, and intra-peritoneal administration, and its presence has been detected in the cerebrospinal fluid and nervous tissue.[49-52]

Curcumin bioavailability has been shown to be considerably enhanced when co-administered with piperine, an alkaloid obtained from black pepper (Piper nigrum) and long pepper (Piper longum).[53] Recently, oral curcumin-piperine combination was clinically evaluated as an adjuvant therapy in COVID-19 patients. Patients receiving curcumin-piperine treatment showed early symptomatic recovery and better clinical outcomes as well as reduced duration of hospitalization.[54] Curcumin as a treatment option against COVID-19 has been a subject of intense investigation since 2020. Investigators utilized *in silico*, *in vitro*, and clinical approaches to study the use of curcumin and its derivatives for its anti-viral, immunomodulatory prophylactic, and therapeutic potential against COVID-19. Since curcumin has been shown to have anti-viral properties, there is a strong rationale for its investigation for the treatment of COVID-19. Curcumin showed anti-viral and anti-inflammatory effects in *in vitro* models of COVID-19. Molecular docking and binding potency studies of curcumin derivatives in *in silico* studies produced encouraging results for the potential use of curcumin derivatives in COVID-19. Curcumin, and its derivatives in various novel dosage forms, have been clinically investigated for their effects on symptoms as well as mortality in COVID-19 patients with encouraging results. Results obtained so far justify the need for further systematic pre-clinical/clinical investigation for the use of curcumin in COVID-19 treatment.[55-59]

Use of nanoparticle-based technology has been featured prominently amongst novel drug delivery systems utilized to improve curcumin bioavailability. Curcumin-loaded nanoparticles have been examined in pre-clinical models, as well as in clinical studies across a wide range of diseases such as neurological disorders, cancers, and parasitic and viral infections, including COVID-19.[60-63] Besides nanoparticle formulations, curcumin has also been formulated and evaluated as liposomes, biodegradable microspheres, micellar formulations, cyclodextrin and phospholipid complexes, and nanogels, as well as metal complexes for enhanced bioavailability and sustained delivery.[64,65] Significant effort has been made in developing drug delivery strategies to develop curcumin as a clinically effective therapeutic agent against a multitude of diseases.[23,64-66] Novel formulations and dosage forms of curcumin need to be evaluated clinically to establish their safety and efficacy.

PERSPECTIVE

The intensely yellow turmeric curcuminoids have been and are still being extensively used in traditional medicine for several ailments. Turmeric remains a popular culinary spice in several cultures and has been shown safe to consume. Pre-clinical studies, both *in vitro* and *in vivo*, have established the antioxidant and anti-inflammatory properties of curcumin. There is significant evidence which shows curcumin's property to modulate a wide range of molecular targets and signaling pathways involved in the pathophysiology of a multitude of diseases.[67-70] In recent years, turmeric curcuminoids and their derivatives have been studied extensively for their therapeutic potential in a range of illnesses such as autoimmune, cardiovascular, endocrine, infectious, metabolic, neurodegenerative, and neoplastic diseases.[49,50,71-74] However, similar to other dietary polyphenols, curcumin has not yet been developed as a clinically available mainstream therapeutic agent. The major caveat in the development of polyphenols as mainstream therapeutic agents is its low bioavailability. The bench-to-bedside transition of polyphenols such as curcumin, resveratrol, and tea polyphenols are difficult as these compounds, both pharmacologically active curcuminoids as well as their reduction and degradation products, show low plasma levels. Using piperine adjuvant therapy is a simple means to enhance curcumin bioavailability. There has been considerable progress in formulating curcumin in novel dosage forms which aim to achieve clinically optimum bioavailability. Clinical development of dosing regimens of curcumin is lacking and requires serious investigation. Rigorous clinical research is needed to establish curcumin as a viable and effective therapeutic agent.

A systematic and vigorous effort is required for turmeric curcuminoids to be utilized as mainstream prophylactic and therapeutic agents. It is important to increase the general awareness of turmeric as a spice and flavoring agent along with its potential health benefits. A critical factor in ensuring curcumin's success as a mainstream therapeutic agent is thorough clinical investigation, which includes dose ranging studies, as well as studies to investigate its safety and efficacy in a wide range of diseases. Collaboration between various governmental agencies, academic institutions, research foundations, as well as the pharmaceutical industry will be most beneficial in ensuring the clinical success for turmeric. General awareness on the potential therapeutic benefits of turmeric curcuminoids is much needed. Dissemination of literature regarding the health benefits of turmeric will be beneficial in increasing the popularity and use of this golden herb.

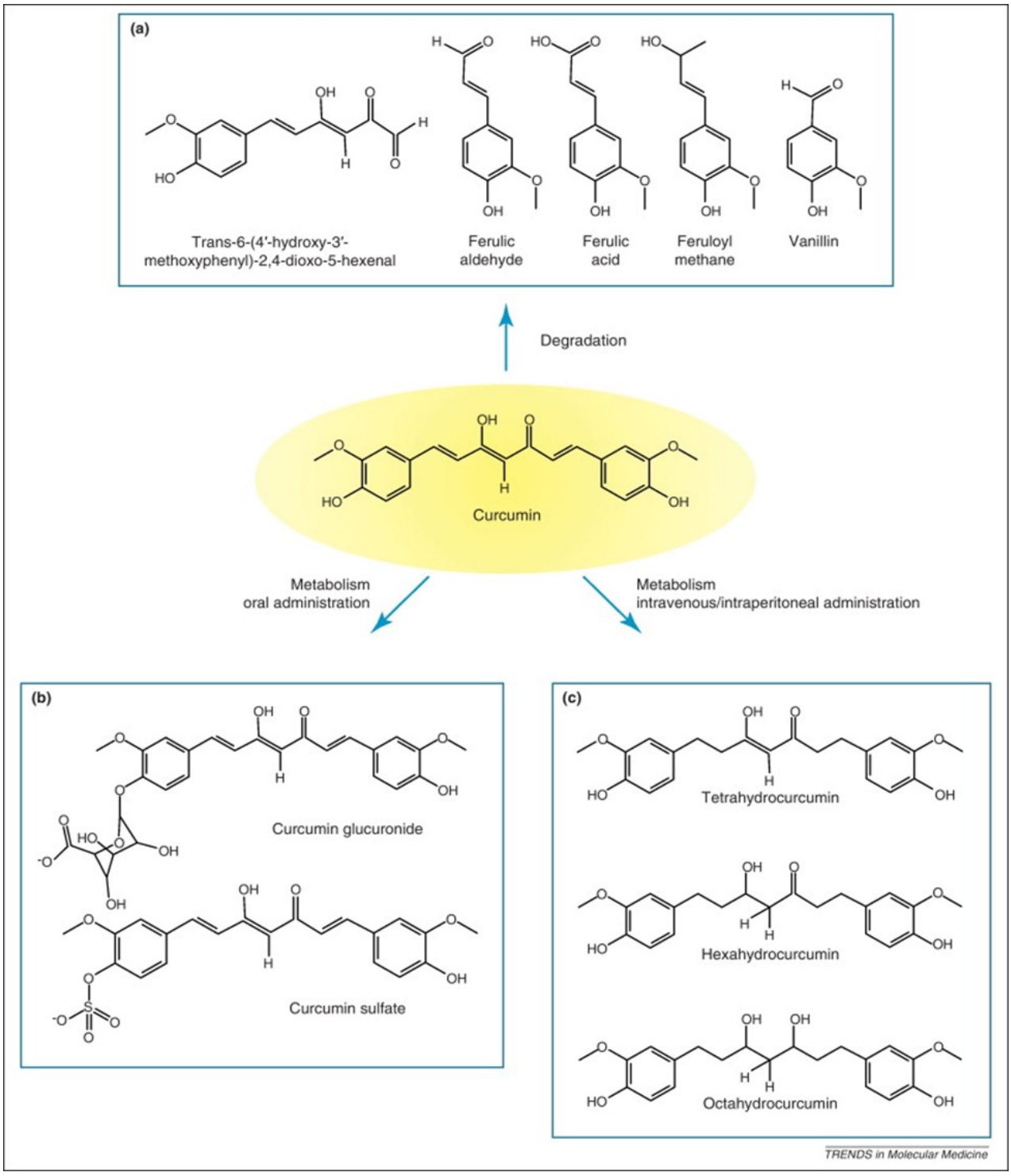

Figure 3. Metabolites of curcumin[48]

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ACKNOWLEDGMENTS

The author gratefully acknowledges the valuable insight and opinions provided by Dr. Moses Oyewumi and Dr. Chris Paxos.

The author expresses his sincere thanks to Dr. Shelley Harrell Ivary for her help with obtaining copyrights for the figures.

CONFLICTS OF INTEREST

All authors declare no conflicts of interest.