Ramesh C. Gupta
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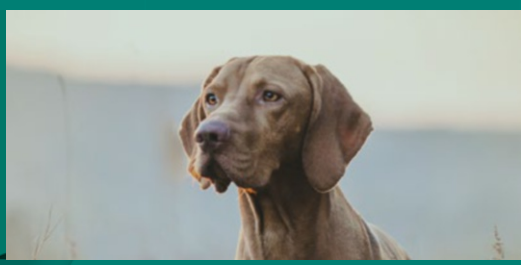

Nutraceuticals in Veterinary Medicine

Springer

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ISBN 978-3-030-04623-1 ISBN 978-3-030-04624-8 (eBook)
https://doi.org/10.1007/978-3-030-04624-8

Dedicated to my wife Denise, daughter Rekha, and parents the late Chandra and Triveni Gupta.

Ramesh C. Gupta

Dedicated to my wife Garima, son Sankalp, daughter Ayana, my mom, my brother Sanjay, and my friends.

Ajay Srivastava

Dedicated to my wife Swati Lall, sons Dr. Rohan Lall and Dr. Rishi Lall, mother Kanak Lata Lall, and late father Professor R.B. Lall.

Rajiv Lall

Introduction

According to the North American Veterinary Nutraceutical Council, a veterinary nutraceutical is defined as "a substance which is produced in a purified or extracted form and administered orally to patients to provide agents for normal body structure and function and administered with the intent of improving the health and well-being of animals." This definition differs slightly from country to country. It seems that nutraceuticals fall somewhere between food/feed nutrients and drugs. Although the herbal medicines have been used for thousands of years in Ayurvedic, Homeopathic, Siddha, Unani, Chinese, Tibetan, Egyptian, Russian, African, Amazonian, and many other systems, by the turn of the twenty-first century, their use became even more popular throughout the world because of their easy access, affordability, and greater tolerability with a wide margin of safety. Outside the USA and Europe, more than 80% of the population relies upon herbal medicines because they are available over the counter and have fewer side effects. Currently, the nutraceutical industry totals more than $250 billion per year, and the use of nutraceuticals in animal health and diseases is more popular than in humans. Due to overriding factors, such as low cost and safety, today's veterinarians may prefer nutraceuticals over modern medicines.

Unlike synthetic pharmaceuticals, nutraceuticals often consist of many bioactive compounds that hit multi-targets and pathways. As a result, nutraceuticals may exert multiple activities, such as free radical scavenging and antioxidative, anti-inflammatory, immunomodulatory, adaptogenic, sedative, antimicrobial, etc., with diverse pharmacological effects (Gupta 2016; Attiq et al. 2018). By having such biological and pharmacological activities, nutraceuticals appear to have wide applications in many human and animal diseases, such as diabetes, hypertension, periodontitis, cognition dysfunction, arthritis, allergies, gastrointestinal, hepatic, renal, cardiovascular, respiratory, genitourinary, and other body organ/system-related dysfunctions, and cancer. A large number of nutraceuticals in the form of prebiotics, probiotics, and synbiotics are used to promote animals' gut health, but appear to favorably influence the functionality of other vital organs as well. By having multiple bioactive constituents, nutraceuticals often provide synergistic effects and impede drug resistance to antibiotics, which is a global health issue (Lillehoj et al. 2018).

In the present world situation, due to the healthcare crisis and dwindling financial resources, the nutraceutical industry faces many challenges. For a large number of nutraceuticals, no data are available on safety and toxicity due to lack of pharmacokinetics, pharmacodynamics, pharmacological, and toxicological studies (Gupta 2016). While some nutraceuticals enjoy the GRAS (generally recognized as safe) status from the US FDA, others pose a toxic threat to human and animal health (Gupta et al. 2018). Due to inadequate quality control, contamination of nutraceuticals with metals, mycotoxins, and inherently toxic plant alkaloids and adulteration with drugs of abuse not only compromise their quality but raise serious health concerns, in addition to giving a bad image to the nutraceutical industry. Patients receiving nutraceuticals also consume therapeutic drug(s), and with the increasing polytherapy trend, adverse interactions and outcomes ensue due to metabolic perturbances from food–nutraceutical–drug interactions (Doorman et al. 2016; Gupta et al. 2018). Furthermore, in many cases, claims for nutraceutical use are either exaggerated or asserted without sound scientific merit.

Nutraceuticals are primarily derived from biological (plants, invertebrate and vertebrate animals, fish, and birds) sources and are well characterized for chemical constituents and biological and pharmacological properties. But, unlike pharmaceuticals, nutraceuticals lack unremitting efforts for the basic core scaffold, mechanism of action (essential and adverse pathways), bioinformatics, pharmacovigilance, structure–activity, dose–response, temporal relationships, and clinical studies.

Unlike modern medicines, nutraceuticals are not strictly regulated in any country. In the USA, the only major regulation related to nutraceuticals is the 1994 passage by the US Congress of the Dietary Supplement Health Education Act. Based on this loosely regulated act, dietary supplements are classified as foods, not dugs, allowing them to be sold without proof of safety and effectiveness (US FDA 1994). However, unlike food, nutraceuticals are not generally recognized as safe, nor can one assume that they are all safe (Gupta et al. 2018). As of now, the FDA's position is clearly asserted that this act does not apply to animals, and the American Veterinary Medical Association (AVMA) does not believe that the act should be modified to include animals (Burns 2017). In the European Union, current regulations require evidence that herbal medicinal products meet acceptable standards of quality, safety, and efficacy before a product license can be issued. Quality control and regulatory guidelines for nutraceuticals, from production, distribution, and national and international trade up to end-user level, appear to vary widely from country to country, and currently they are not strictly adhered to as for pharmaceuticals.

At recent national and international conferences (American Veterinary Medical Association, International Veterinary Congress, World Veterinary Association Congress, European nutraceuticals, and many others), a large number of veterinarians, nutritionists, food scientists, and animal health professionals recognized the importance of nutraceuticals for animal health and diseases. Accordingly, *Nutraceuticals in Veterinary Medicine* has been prepared to meet the challenges of today's veterinarians, pet lovers, animal health professionals, farm animal producers, and the veterinary nutraceutical industry. The book contains more than sixty chapters, arranged under seven sections. Each chapter is prepared using a very user-friendly format to provide scientific insight for academicians and veterinary practitioners with an interest in animal nutrition, complementary veterinary medicine, and nutraceutical product development and research.

The factual statements are substantiated with pertinent references for further reading. Some chapters are prepared from the one health perspective, encompassing animal and human health and experimental studies.

Following a brief introduction, the book begins with Section I on common nutraceuticals that are used in the formulations of hundreds of nutraceutical products. This follows Section II on prebiotics, probiotics, synbiotics, enzymes, antibacterial alternatives, and feed additives. The bulk of this book (20 chapters) lies in Section III that deals with nutraceuticals in organ/system-related diseases and disorders. Section IV covers chapters devoted to nutraceuticals for specific species including cattle, equine, camelids, and poultry. This follows Section V on safety and toxicity evaluation of nutraceuticals and functional foods using *in vitro*, *in vivo*, and other models, biomarkers for selected foods and nutraceuticals, and toxic interaction of nutraceuticals with foods and pharmaceuticals. Section VI deals with newer trends in nutraceutical research and product development covering chapters on proteomics and foodomics, nanoparticle-based bioavailability of nutraceutical ingredients and nanosupplements, and veterinary nutraceuticals stability testing. Lastly, Section VII extensively covers chapters on regulatory aspects of nutraceuticals in different continents and countries, including North America, the European Union, India, China, Australia, New Zealand, Turkey, the Philippines, and South Africa. *Nutraceuticals in Veterinary Medicine* is the most comprehensive book in the field of veterinary nutraceuticals, and it offers many chapters on novel topics that are not

covered in any previously published book. This book will serve academia, industry, and government sectors alike.

The editors remain grateful to the contributors of this book from many countries (the USA, Australia, Canada, China, India, Philippines, Russia, Saudi Arabia, South Africa, Turkey, and the UK) for their hard work and dedication. These authors are highly qualified and trained in diverse disciplines (veterinary medicine, nutrition, food science, animal science, pharmacology, toxicology, molecular biology and technology, omics, chemistry, biochemistry, and others), who shaped this book using a framework of integrative approach. The editors would like to thank Ms. Annette Klaus, associate editor, Mr. Bibhuti Sharma, project coordinator (Springer Nature), and Ms. Krithika Shivakumar, project manager, for their untiring support in the production of this book. Last but not least, the editors would also like to thank Ms. Robin B. Doss for critically checking the text and references.

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Part I

Common Nutraceuticals

Standardized Turmeric and Curcumin

Naresh Chand

Abstract

Turmeric root is an ancient Ayurvedic herb, and it is used as a spice, and in very low doses, it may modulate immune-inflammatory diseases of the gut, joints, brain, and body in turmeric-consuming part of the world. Turmeric contains more than 235 active ingredients including essential oils, curcuminoids (>89), and turmerosaccharides as well as curcuminoid-free ingredients and fiber. These phytochemicals and fiber as well as their metabolites and products of microbial degradation may act in additive or synergistic fashion as a modulator of persistent dysregulated chronic immune inflammation and pain in horses, pets, and people. The limited preclinical data support that low doses of turmeric or its active ingredient (curcumin/curcuminoids) may have modulatory applications in preventing or treating immune-inflammatory diseases of the eyes, brain, joints, and gut in pets and people. The standardized turmeric (ST) is a novel concept; it is based on a recently filled patent. ST may reduce the need for analgesics (opiates), antidepressants, steroids, and anticancer medications. Using the latest drug-targeted delivery and reliable clinical trial strategies, ST may be considered for R&D for the prevention and treatment of OA, dementia, and other age-related diseases of the eyes, brain, gut, and joints in pets and humans. The consumers need to be aware of the adulterations of turmeric and its extracts.

Keywords

Standardized turmeric · Curcumin · Modulator of persistent dysregulated chronic immune inflammation and pain · Pets

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1 Introduction

Turmeric is the dried rhizome (root) from three major varieties of the *Curcuma longa* plant—*Curcuma aromatica* (wild turmeric, South Asia), *Curcuma wenyujin* (China), and *Curcuma domestica* (Thailand). It is an herbaceous perennial plant which belongs to the ginger family, *Zingiberaceae*. Turmeric is native to Southeast Asia particularly to the Indian subcontinent. It is cultivated in India, China, Thailand, Indonesia, Japan, and other tropical regions including Africa (Gopinath and Karthikeyan 2018). More than 133 different species of turmeric have been identified (Prasad and Aggarwal 2011). The composition of turmeric has been summarized in Table 1. Turmeric root contains curcuminoids, curcumin-free ingredients, essential oils, water-soluble turmerosaccharides, and fiber. The amount of medicinal ingredients such as curcumin/curcuminoids in turmeric powder may vary considerably from region to region (Ashraf et al. 2015). This may depend on the species, phylogenetic and epigenetics of the turmeric plant, cultivation practices, soil nutrition, rainfall, and sun exposure, as well as different extraction methods. Native turmeric's more than 235 complex phytochemicals naturally assemble in the roots and may exert additive or synergistic health beneficial effects (Aggarwal et al. 2013; Javeri and Chand 2016; Li et al. 2011). Turmeric may be considered the "poor man's aspirin" as it is available in every Indian home and is affordable as food (spice).

Pulverized turmeric root is an ancient Ayurvedic herb (spice) often used for cosmetic, religious, and spiritual festivities as well as for flavoring and coloring foods in traditional cooking. It is also used as a traditional herbal medicine since ancient times in India and other turmeric-consuming parts of the world. In addition, small quantities of turmeric are used two or three times a day as a flavoring spice in the Indian subcontinent and Southeast Asia. Turmeric alone, or in combination with other herbs, is seasoned by frying in cooking oil or ghee (clarified butter) before

R. C. Gupta et al. (eds.), *Nutraceuticals in Veterinary Medicine*, https://doi.org/10.1007/978-3-030-04624-8_1

Table 1 Composition of turmeric and major curcuminoids

Turmeric constituents		Curcuminoids	
	% (w/w)		%
Curcuminoids	1.4–5[a]	Curcumin	60–70
Essential oils	3–7	Demethoxycurcumin	20–27
Fiber	2–7	Bismethoxycurcumin	10–15
Minerals	3–7		
Fat	5–10		
Protein	6–8	Turmerosaccharide	10
Carbohydrate	60–70		
Moisture	6–13		

Modified after Nelson et al. The essential medicinal chemistry of curcumin. Mini-perspective. J Med Chem 60, 1620–1637
[a]Ashraf et al. (2015)

adding beans, grains, rice, and vegetables. This method is part of the lipidation (solubilization), activation, and stabilization of turmeric's active ingredients. It is used as food, and it may offer some health benefits in early stages of chronic diseases. This ancient formulation method (may resemble to nanotechnology of the modern era) is used in traditional Indian kitchens. It may improve the bioavailability of phytochemicals in turmeric. The traditional Indian kitchen is a living and functional polypharmacy. Turmeric use has been described to prevent food and lung allergies, aches, pain, flu, common cold, skin wounds, and digestive and other disorders; it has been used to overcome the effects of concussions (TBI) and has been used in many herbal formulations (>800) in dietary supplements for prevention of a wide variety of diseases (Gopinath and Karthikeyan 2018). The safety and efficacy of these combinations (nutraceuticals or dietary supplements on the market) have not undergone rigorous testing in animals and people suffering with immune-inflammatory diseases of the joints, gut, and brain.

The health benefit of turmeric or its active ingredients, such as curcumin, may be more pronounced during early disease states (Javeri and Chand 2016; Sundaram et al. 2017; Kumar et al. 2018). Therefore, turmeric or curcuminoids and other ingredients are likely to be part of the preventive strategies rather than a cure. Standardized turmeric (meaning containing 1.4, 3, 5% curcumin, Chand 2018) and other ingredients at low doses may be used as an adjunct therapy in the management of dysregulated persistent chronic immune-inflammatory diseases of the musculoskeletal, gastrointestinal (digestive), pulmonary, cardiovascular, and nervous systems.

Ayurveda is an ancient art of restoring "homeostasis" under early disease states. It proposes that the amount of spice or its active ingredient(s) does not follow a perfect relationship to effectiveness (pharmacokinetics/pharmacodynamics (PK/PD) modeling)—meaning that more is not better. Preclinical studies in Alzheimer's mouse models support this concept (Lim et al. 2001; Begum et al. 2008). In fact, the opposite situation may occur at higher doses, meaning higher dose may negate its own health benefits (Dr. Frautschy UCLA; personal communication). One of the Ayurvedic medicine's basic principles is that efficacy cannot be related to plasma levels of a major ingredient in a spice (herb), and the whole herb is often more efficacious than its individual ingredients. In most preclinical studies, the distribution of active ingredient(s) of turmeric to site of action (inflammation or disease states) is not carefully investigated. The active ingredients of turmeric seem to be preferentially delivered to the site of inflammation (personal observation) and the brain of mice with progressive Alzheimer's disease state (Begum et al. 2008).

Curcumin, chemically known as (1*E*, 6*E*)-1,7-bis (4-hydroxy-3-methoxyphenyl) hepta-1,6-diene-3,5-dione, is a highly pleiotropic natural polyphenolic chemical (Fig. 1). Recently, Kumar et al. (2018) summarized the potential use of curcumin in aging-related diseases. Curcumin is one of the active ingredients in the spice turmeric—a routinely used spice in traditional Indian cuisine. Curcumin is known to exert numerous in vitro and in vivo pharmacological activities in experimental animals often at relatively high doses (concentrations). The broad pharmacological profile of curcumin in experimental animals tends to suggest that it may exert health beneficial effects; however, clear clinical evidence of efficacy in any disease state is still lacking.

Over the past decade, the field has made enormous progress in improving the bioavailability of curcumin (Gopi et al. 2017). In addition to improvement of curcumin's bioavailability (pharmacokinetics), high doses of curcumin were utilized in most clinical trials conducted so far. Neither improvement of bioavailability nor increased dose improved curcumin's efficacy in Alzheimer's disease in humans (Mazzanti and Di Giacomo 2016). This is in agreement with the Ayurvedic principle—more of one active ingredient is not better (Begum et al. 2008; Chand 2018).

The chemical structure of major curcuminoids—curcumin, demethoxycurcumin, and bisdemethoxycurcumin—and major metabolites of curcumin is shown in Fig. 1.

Curcumin is an unstable, reactive, and non-bioavailable physiochemical, and therefore it is not a lead candidate for R&D. This concept is likely to be true when high "astronomical" doses of curcumin are utilized in animals or patients, but low doses of standardized turmeric or curcumin may present R&D opportunities which should be explored. In this book chapter, I (as a lifelong Ayurvedic scholar and an R&D pharmacologist since 1981) take a different perspective on this subject matter of great economic and healthcare importance for aging populations. Standardized turmeric (containing 3, 9, 27, or 81 mg curcuminoids) taken with

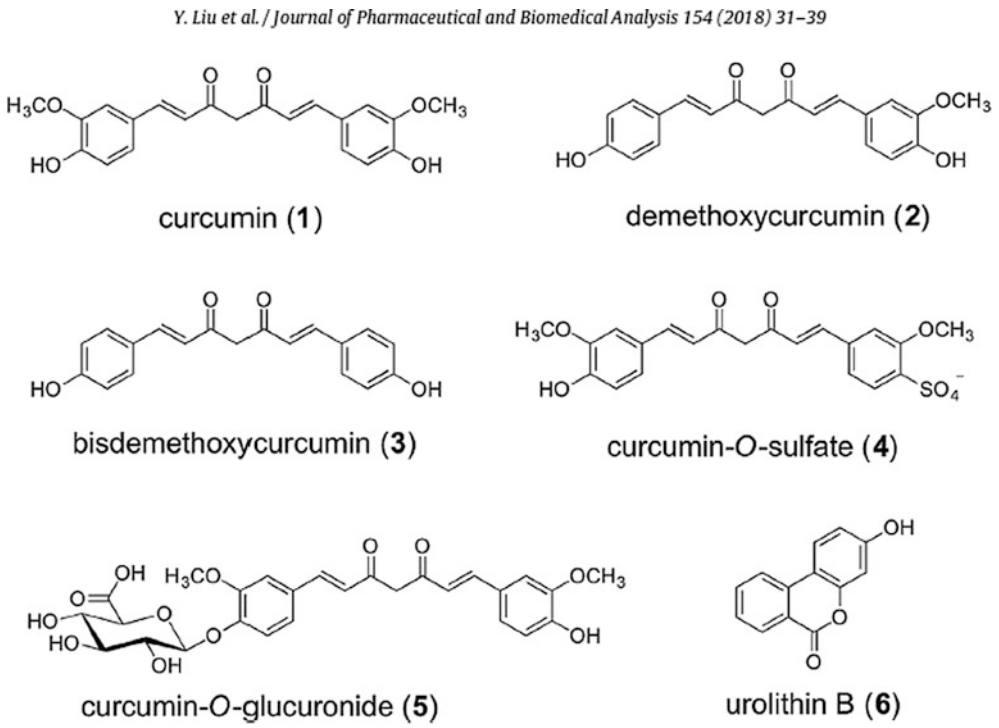

Fig. 1 Chemical structures of curcumin (**1**), demethoxycurcumin (**2**), bisdemethoxycurcumin (**3**), curcumin-*O*-sulfate (**4**), curcumin-*O*-glucuronide (**5**), and the internal standard, urolithin B (**6**)

food two to three times a day for life may have some long-term potential for slowing the age-related progression of chronic diseases in pets, including horses, and people. This chapter described the effects of turmeric or low doses of curcumin in animals, which may have some clinical relevance in the prevention of chronic illnesses of the joints, digestive system, eyes, brain, etc.

Curcumin may act as an immune modulator (Mollazadeh et al. 2017). Low doses of standardized turmeric or curcumin (curcuminoids) taken as a dietary supplement (as food/spice) for long duration (lifelong exposure) may exert modulation of immune inflammation in many chronic disease states including chronic pain, inflammatory bowel disease (IBD), osteoarthritis, and Alzheimer's disease (Javeri and Chand 2016; Lim et al. 2001; Begum et al. 2008; Sundaram et al. 2017). Furthermore, turmeric, which contains diverse and complex phytochemicals (>235; 69 curcuminoids), may serve as a preventive (modulatory) agent or as an adjunct therapy. It may reduce the need for medications such as opiates, NSAIDs, steroids, antiarthritic, or anti-gout, as well as anticancer agents. In other words, low doses of ST, especially when taken as a spice (herb in low doses) added to foods on regular basis—rather than in a pill (capsule)—may act as an adjunct therapy in many diseases with underlying dysregulated persistent chronic immune inflammation in aging pets, horses, and people.

The products of bioactive degradation and microbial metabolism of curcuminoids, polysaccharides, curcumin-free phytochemicals, and fiber in the digestive system may exert regulatory effects on genetics, epigenetics, protostomes, and function of microbiota in the digestive system. The photochemical metabolites from the liver and microbiota processing may exert additive or synergistic activity in modulating the gut-immune-brain axis, the colon and its surroundings—permeability and barrier functions of epithelium in immune-inflammatory diseases of the gastrointestinal tract and infections, constipation, and diarrhea. In Ayurvedic medicine, mild laxative effects of turmeric or ST and its interaction with microbiota in the digestive system have been suggested to improve gut-brain functioning (Shen et al. 2017).

Low doses of turmeric (~200–300 mg, once a day, BID) and curcumin (~3–30 mg once a day, BID, in foods) are often considered safe. In addition, many people in non-turmeric-consuming nations may be using too much of these dietary supplements—curcumin (curcuminoids) and turmeric alone or in combination with other dietary supplements and medications. They may not be benefiting from using these higher doses, and in fact, some may face adverse consequences, especially among seniors taking three to ten medications. Such drug-drug interactions remain to be evaluated. The efficacy and safety of standardized turmeric (ST) in disease states in pets and people taking various other medications or supplements is warranted. The level of various ingredients at the inflammatory site or brain or in cancer tissues in the disease states in dogs, cats, or horses may

offer better understanding of the absorption, distribution, metabolism, and excretion (ADME; pharmacokinetics—PK) and drug delivery issues in using herbs (nutraceutical "dietary supplements") in foods as well as adjunct medicine. The long-term use of low doses of ST as an oral supplement or as nanoparticles in disease states in pets and people may help in lowering the doses of medications such as NSAIDs, opiates, steroids, anticancer, anti-gout, anti-RA, and CNS-acting drugs. Thus, ST and other formulations of curcumin (curcuminoids, turmerosaccharides, curcumin-free phytochemicals) may exert sparing effects on morphine, steroids, and other medications.

2 Chemical Composition

Jia et al. (2017) reviewed and offered details about the chemical constituents of turmeric. It contains curcuminoids, steroids, terpenoids, flavonoids, and phenylpropene derivatives and alkaloids. The major curcuminoid (curcumin) has been extensively studied in preclinical animal models. In addition to turmeric's three major curcuminoids, there are several minor curcuminoids, which may exert significant bioactivities. They identified 89 curcuminoids in the turmeric samples using ultrahigh-performance liquid chromatography—quadrupole time-of-flight tandem mass spectrometry. Ashraf et al. (2015) demonstrated that content of curcuminoids in turmeric varies significantly from region to region of India (1.4–5.0%).

Commercially available curcumin contains at least three curcumin compounds including curcumin, demethoxycurcumin (DMC), and bisdemethoxycurcumin (BDMC) in a ratio of 66, 23, 11, respectively.

3 Turmeric Consumption

Prasad and Aggarwal (2011) summarized multiple uses of turmeric in Asian cuisine and its consumption. It is used as a preservative and antimicrobial agent and is used in making pickles (mango, limes, lemons, and others) and savory and sweet dishes and is widely used in Eastern cooking specialties. The consumption of turmeric in Asian countries in humans is in the range of 200–1000 mg/day (160–440 g/person/year, often costing less than $1 dollar). Intake in urban areas is lower (200 mg/day/person) than in rural areas (600 mg/day/person). This information may be used in translational sciences, meaning the consumption of curcumin from turmeric in Asian countries in humans is in the range of 2.8–30 mg/day (average of 15 mg/day; Chand 2018). In the USA, most people (healthy enthusiasts) are using 1–5 g of turmeric every day which is >5–25 times of that used in India. High doses of herbs often act as prooxidant and pro-inflammatory. Because of high consumption and demand for turmeric in Western countries, the adulteration with lead and other products has become a common practice.

3.1 Safety

Turmeric use (low dose) as a spice in food is safe for human consumption. However, high doses may alter taste and disturb gastrointestinal functions leading to nausea, diarrhea, and vomiting. Gupta et al. (2013) summarized that curcumin is safe in rodents, primates, horses, rabbits, cats, and humans. Curcumin inhibits the activity of drug-metabolizing enzymes such as cytochrome P450, GST, and UDP-glucuronosyltransferase in vitro and in animal models. Therefore, the possibility exists that drug-drug interaction in patients taking medications such as acetaminophen, digoxin, and morphine may increase the plasma concentrations after curcumin dosing. This may lead to potential drug safety concerns. Curcumin is an active iron chelator and induces anemia in mice fed iron-poor diets. These possibilities such as GI effects—nausea, diarrhea, and vomiting—anemia, and bleeding, under some circumstances, need to be kept in mind while advancing the R&D on standardized turmeric and curcumin (Gupta et al. 2013; Chand 2018).

It remains to be explored if standardized turmeric (containing >235 phytochemicals, essential oils, and fiber) offers better efficacy and safety than curcumin alone.

4 Pharmacokinetics

Despite a vast amount of publications on curcumin, detailed oral pharmacokinetic studies using turmeric and curcumin/curcuminoids (many formulations and brands) are still lacking. Following the latest PK/PD modeling and analytical techniques, detailed oral pharmacokinetic studies using turmeric or curcumin/curcuminoids (many formulations and brands) in the blood (cells) and tissues of cats, dogs, and horses living with chronic immune-inflammatory diseases are warranted. Such investigations would help in finding safe, effective, preventive, and therapeutic nutraceuticals for many diseases of pets and people.

Curcumin is insoluble in aqueous media; is unstable under conditions of ambient light, room temperature, and basic pH; and is readily metabolized or degraded upon oral dosing (Matabudul et al. 2012). Limited pharmacokinetic studies in mice (Begum et al. 2008), rats (Suresh and Srinivasan 2010), dogs (Bolger et al. 2017, 2018; Matabudul et al. 2012), and human (Schiborr et al. 2014; Small et al. 2017; Bolger et al. 2018) have been reported. Matabudul et al. (2012) studied

PK profiles following prolonged intravenous infusion of curcumin (10 mg/kg lipocurc™, either over 2 h or over 8 h) in dogs. The ratio of tetrahydrocurcumin (THC)/curcumin was highest in hippocampus > brainstem > striatum > spleen. Based on the data obtained in this study, they raised the possibility that this formulation may facilitate distribution into tissues via a transporter-dependent mechanism and that elevated tissue concentrations of curcumin may inhibit or saturate a putative reductase enzyme converting curcumin to THC in the body.

Bolger et al. (2017) investigated the distribution of curcumin (Lipocurc™) and its major metabolite tetrahydrocurcumin (THC) in dog (Beagles) and human red blood cells, peripheral blood mononuclear cells (PBMC), and hepatocytes. They observed a good correlation between the species differences of red blood cell metabolism of curcumin to THC and in vivo plasma levels of curcumin and THC from clinical studies. They found that curcumin's distribution into, and metabolism by, red blood cells significantly impacts the ADME (pharmacokinetics) of curcumin. They reported many species-related differences in distribution of curcumin and THC in dogs and humans. The metabolism of curcumin to THC was similar. Curcumin distribution into PBMC from patients with chronic lymphocytic leukemia (cancer) was higher compared to PBMC from healthy individuals. The greater distribution of curcumin into PBMC in patients with cancer may have therapeutic advantage (Bolger et al. 2018).

Suresh and Srinivasan (2010) studied pharmacokinetics following oral administration of piperine (170 mg/kg) and curcumin (500 mg/kg) in rats. The tissue concentrations of curcumin and piperine were determined by HPLC. Curcumin's bioavailability was 63.5% with a C_{max} at 1 h (intestine) and 6 h (blood) and remained at significantly higher level even at 24 h. Only a small portion of curcumin (0.2%) was excreted in urine. Concomitantly oral administration with piperine improved curcumin's intestinal absorption and stayed significantly longer in the body tissues. Curcumin was detected in the brain at 24, 48, and 96 h with a maximum at 48 h. They concluded that curcumin could be traced in the brain following its oral administration, and its bioavailability can be improved by co-administration with piperine. The long-term clinical studies using turmeric or curcumin at low doses are needed in pets, horses, and people.

Schiborr et al. (2014) conducted a randomized small crossover study in healthy subjects (13 women, 10 men). A single oral dose of 500 mg curcuminoids as native powder, micronized powder, or liquid micelles was utilized. Blood and urine samples were collected for 24 h, and total curcuminoids and safety parameters were quantified. In the area under the plasma concentration-time curve (AUC), micronized curcumin indicated 14-, 5-, and 9-fold and micellar curcumin 277-, 114-, and 185-fold better bioavailable than native curcumin in women, men, and all subjects, respectively. Curcumin was better absorbed in women than men. Both the micronized powder and, in particular, the liquid micellar formulation of curcumin significantly improved its oral bioavailability without altering safety parameters. The liquid micellar formulation of curcumin or nanoparticle may be well suited to deliver curcumin in human intervention trials. All safety parameters remained within the reference ranges following the consumption of these formulations. The observed differences in curcumin absorption (pharmacokinetics) warrant further ADME investigation in pets and horses of both genders.

5 Mechanism of Action

The precise mode of action for turmeric and curcumin (curcuminoids) remains unknown. Javeri and Chand (2016) and Kumar et al. (2018) summarized that curcumin may act via multiple modes of action. It may act as modulator of dysregulated immune inflammation. Curcumin is well known to influence many genes, epigenetic steps, enzymes, and pathways. This profile may be relevant to its broad spectrum of pharmacology (Javeri and Chand 2016; Cavaleri 2018; Kumar et al. 2018; McCubrey et al. 2017).

Colitti et al. (2012) evaluated the effects of dietary curcumin (CurcuVet, 4 mg/kg BID for 20 days, $n = 6$) and compared it with NSAID (firocoxib, 5 mg/kg BID for 20 days, $n = 6$) in dogs suffering with osteoarthritis (OA). This small clinical trial was designed to study the effects of NSAID or dietary administration of curcumin on canine transcriptome using circulating leukocytes. This study highlights the complexities of mode of action of curcumin on gene level using a chronic disease model. At the end of the treatment on day 20, a reduction of pain and a partial recovery of articular function were observed by the veterinarians. On day 20, these investigators discovered that curcumin treatment reduced 228 downregulated genes to 110 and reduced 271 upregulated genes to 31. Treatment with curcumin (CurcuVet, 4 mg/kg BID for 20 days, $n = 6$) altered gene expression, inhibited macrophage proliferation, downregulated genes involved in inflammatory response (TNFα, TLR4, IL8, IL18, and MAPK14), and upregulated Ikβ in the TNRF1 signaling pathway (improving communication between immune cells), as well as activated genes involved in fibrinolysis. However, NSAID upregulated genes (TNFα, TLR4, IL8) but did not influence genes (IL18 and Ikβ) in the TNRF1 signaling pathway. These findings show differential modulation of genes by curcumin and NSAID. A long-term large clinical trial is warranted in aging cats, dogs, horses, and people suffering with OA and other dysregulated chronic immune-inflammatory diseases of the joints, brain, eyes, and digestive system. In this study, the effect size was highly variable. These investigators

concluded that due to the small number of dogs (six) in the study and highly variable clinical effect size, the clear proof of clinical efficacy could not be established.

In the brain, diverse mechanisms of action may involve modulation of transcription pathways, protostomes, neurogenesis, and the hypothalamic-pituitary-adrenal axis as well as immune inflammatory pathways (Seo et al. 2015). The potential antiarthritic effects of turmeric or its extracts may be related to the establishment of equilibrium between catabolism and anabolism of joint cartilage as well as its well-known broad spectrum of anti-inflammatory activities. In 2016, de Oliveira et al. provided evidence that curcumin improves mitochondrial dynamics—mitochondrial biogenesis and mitophagy (a key step in keeping the cell healthy). They also elegantly summarized curcumin biosynthesis, source, bioavailability, and metabolism.

The long-term effect of turmeric- or curcumin-containing dietary supplements (nutraceuticals) and medications using wide dose ranges and longer duration of treatment on gene transcription (expression and function in circulatory leukocytes or at the site of inflammation such as the joints or the brain) in horses, pets, and patients living with specific diseases may offer reliable, reproducible, and viable biomarkers of clinical efficacy and safety. This knowledge may help the R&D experts in discovering and formulating safer and effective combination(s) of herbs or their active ingredients.

6 Digestive System

Inflammatory bowel disease (IBD), a chronic immune disorder of the digestive system, is very common in cats and humans. IBD can be divided into two subgroups: Crohn's disease (CD) and ulcerative colitis (UC). The current pharmacological approaches for treating IBD are generally not curative and are often associated with serious side effects. The disease-altering medications, such as thiopurines, methotrexate, tacrolimus, thalidomide, cyclosporine, and infliximab, are expensive. Brumatti et al. (2014) and Neto et al. (2018) have reviewed and summarized the pathogenesis of IBD and its current therapeutic approaches and potential therapeutic utility of curcumin. Often there is a strong relationship between nutrition and IBD pathogenesis. Therefore, developing new dietary strategies using turmeric or its active phytochemicals such as curcumin may open a door for finding an affordable adjunct therapy and prevention approach for the early stages of IBD. They concluded that it is necessary to find the suitable dose of curcumin and optimal duration of treatment for preventing or treating the recurrence of IBD. Turmeric or its active ingredients may act by decreasing the mucosal immune inflammation and dysbiosis in acute and chronic IBD.

Turmeric has been used in Ayurvedic and traditional folk medicine in the management of inflammatory disorders including IBD. Therapeutic concentration of turmeric and its active ingredients such as curcumin may be achieved in the gastrointestinal tract after oral dosing. This may make it a good candidate for the prevention and treatment of IBD (Hanai et al. 2006; Brumatti et al. 2014; Lang et al. 2015; Neto et al. 2018; Bastaki et al. 2016; Yang et al. 2018). Poor aqueous solubility, poor absorption, bio-distribution, rapid metabolism, and fast elimination of curcumin may cause limitations in its clinical development (Brumatti et al. 2014; Javeri and Chand 2016). However, this profile may be desirable for R&D for IBD. It remains to be discovered if standardized turmeric may overcome such challenges in treating digestive diseases (IBD and diarrhea) in cats, dogs, and people.

Bastaki et al. (2016) evaluated the effect of turmeric on colon histology, body weight, ulcer, IL_{23}, MPO, and glutathione in acetic acid-induced IBD in rats. Turmeric powder (1, 10, and 100 mg/kg/day) was administered orally for 3 days before or 30 min after the induction of IBD. This treatment was found to reduce macroscopic and microscopic ulcers, IL_{23}, myeloperoxidase, and GSH (reduced glutathione peroxidase). The lowest dose of turmeric (1 mg/kg) caused a significant decrease in mean macroscopic ulcer and score after day 7, when compared to untreated groups. Interestingly a high dose (100 mg/kg) also caused a significant (~50%) reduction after 2 days. High dose had no significant effect on mean macroscopic ulcer and score after 4 and 7 days of IBD. They also observed that this treatment increased body weight and reduced colitis-related oxidative stress. The 10 mg/kg dose appeared to be the ideal dose in rat IBD model. These investigators suggested a possibility of developing *C. longa* (turmeric) as a safe and potent anti-inflammatory and antioxidant herbal remedy in the management of IBD.

Hanai et al. (2006) studied the effect of curcumin on ulcerative colitis (UC). Patients suffering with UC were given sulfasalazine (1.0–3.0 g/day) or mesalamine (1.5–3.0 g/day) plus 2 g curcumin (1 g taken after breakfast and 1 g after the evening meal), or placebo, for 6 months. Patients were then followed for an additional 6 months, during which either SZ or mesalamine was continued. All medications except SZ or mesalamine were discontinued 4 weeks before starting this study. Eight of 39 patients in the placebo group relapsed, whereas 2 out of 43 patients on curcumin relapsed during the 6 months of therapy. These authors concluded that curcumin may be a safe and effective medication for maintaining remission in patients with Crohn's disease or UC. In another study, IBD patients were given curcumin (360 mg/dose) three to four times a day for 3 months. This treatment significantly reduced clinical relapse in patients with quiescent IBD. The inhibitory effects of curcumin on inflammatory mechanisms like NF-κB, COX_2, LOX, and TNFα and its safety profile suggest that

curcumin or turmeric may have some prospects in the treatment of IBD. They recommended that randomized controlled clinical investigations in large cohorts of patients are warranted to fully evaluate the clinical potential of curcumin (Hanai and Sugimoto 2009). Similar well-designed long-term clinical studies using turmeric or its active ingredients need to be conducted in cats and dogs suffering from digestive diseases such as diarrhea and IBD.

Later, Lang et al. (2015) demonstrated that the addition of curcumin to mesalamine was superior to the combination of placebo and mesalamine in inducing clinical and endoscopic remission in patients with mild-to-moderate active UC. Patients received 1 month of add-on therapy of 3 g oral capsules of curcumin or an identical placebo in two divided doses daily (consisting of three capsules twice a day before meals). This addition did not produce any apparent adverse effects. They concluded that curcumin may be a safe and effective agent for the management and treatment of UC.

Shen et al. (2017) evaluated the effects of oral curcumin administration on the gut microbiota of C57BL/6 mice. Curcumin significantly affected the abundance of several representative families in gut microbial communities including Prevotellaceae, Bacteroidaceae, and Rikenellaceae. Dou et al. (2018) studied the effect of curcumin (100 mg/kg/day PO for 14 days) on collagen-induced arthritis (CIA) in rats. They demonstrated that curcumin attenuates CIA through modulating the function of the cholinergic system in the gut-brain axis.

Yang et al. (2018) administered curcumin or tetrahydrocurcumin orally (0.1 or 0.25 mmol/kg daily) for 7 days before and together with dextran sulfate sodium (DSS administration, 3% in tap water) in mice. Oral dosing of curcumin significantly reduced the severity of DSS-induced colitis. This treatment also reduced the activation of NF-ϰB and STAT3 as well as expression of COX-2 and inducible nitric oxide synthase. Tetrahydrocurcumin exerted weak inhibitory effects. This group of scientists concluded that oral administration of curcumin inhibits experimentally induced murine colitis. This effect was associated with inhibition of pro-inflammatory signaling mediated by NF-ϰB and STAT3.

Ohno et al. (2017) studied the effect of nanoparticle curcumin on the development of DSS-induced colitis in mice. The rodent diet was mixed with nanoparticle curcumin (0.2%). The administration of nanoparticle curcumin was started 7 days before DSS administration. This treatment significantly improved mucosal permeability and reduced body weight loss, disease activity index, and histological colitis score. This treatment significantly reduced NF-κB activation in colonic epithelial cells and mucosal mRNA expression of inflammatory mediators and increased the abundance of butyrate-producing bacteria and fecal butyrate level. This was accompanied by increased expansion of CD4 + Foxp3+ regulatory T cells and CD103+ CD8α− regulatory dendritic cells in the colonic mucosa. They concluded that nanoparticle curcumin may be a promising candidate as a therapeutic option for the prevention and treatment of IBD.

McCann et al. (2014) demonstrated that turmeric, partly due to its curcumin content, exerts a beneficial effect on two gene variants linked to IBD severity. Turmeric reduces the abnormal transport function of the SLC22A4 503F variant (authenticated cell lines Flp-In™ 293 (Flp293) and 293/TLR4-MD2-CD14). It also increases the activity of the IL_{10} promoter variant, which was reduced in IBD. They suggested that IBD sufferers with the defective gene variants may benefit from turmeric consumption. These in vitro observations suggest a need for conducting long-term clinical studies using standardized turmeric and/or other curcumin formulations in pets, horses, and people suffering with IBD.

Bland et al. (2017) studied the effects of liposomal curcumin on five opportunistic bacterial strains in the equine hindgut. Horses often suffer gastrointestinal (GI) tract illnesses such as colic, enterocolitis, diarrhea, and inflammatory bowel disease. The intestinal tract in horse is sensitive and contains a highly complex microbial population. Infections, immune inflammation, and colic may occur as a result of a shift in the microbial population, or dysbiosis. The use of nutraceuticals in the equine industry is on the rise, and curcumin possesses antimicrobial properties that may help in minimizing the proliferation of opportunistic bacteria. *C. perfringens*, *C. difficile*, *E. coli* in general and K-12, and *Streptococcus bovis/equinus* complex (SBEC) are common opportunistic bacteria found in the hindgut of horses. Liposomal curcumin at higher doses has the potential to increase the concentration of opportunistic bacteria, which would contribute to microbial dysbiosis rather than mitigate it. The use of standardized turmeric or its active ingredients as nanoparticles, and a wide range of low doses with a longer treatment period, may restore homeostasis in the gastrointestinal system during disease states such as enterocolitis, diarrhea, and inflammatory bowel disease and dysbiosis. It may exert antimicrobial properties without adversely affecting cecal characteristics.

Turmeric, or its curcuminoids (curcumin) and other active ingredients, may slow the progression of dysregulated persistent chronic immune inflammation in the wall of the intestine if the treatment is started in the early stages of IBD. The regular use of low doses of turmeric or its extracts as dietary supplement or as spice (as food) may also reduce the need for disease-altering medications in the gastrointestinal tract. Clinical long-term studies using a wide dose range of turmeric or curcumin in pets, horses, and people living with mild-to-moderate IBD are warranted.

In conclusion, curcumin, or its novel nano-formulations, or standardized turmeric (containing >235 phytochemicals, fiber, and their degradation products by the gut microbiota)

may alter permeability and epithelial barrier function of the gastrointestinal (GI) tract by altering the macro- and micro-environment in IBD (UC and CD) in cats, dogs, and people. Turmeric, or its active ingredients' broad spectrum of the mechanism of action, especially under immune inflammatory states in the gastrointestinal tract, may restore homeostasis and may slow the progression of IBD, if treatment is started in the early stages.

7 Common Cold and Infections

Cats and dogs often suffer from ear, skin, urinary, and bladder infections and common cold. The anti-inflammatory, antibacterial, and antiviral activities of turmeric and curcumin may help in preventing or treating infection in pets and people. Kennel cough (common cold) is common in cats and dogs. There is a need for finding natural products or extracts to deal with the emergence of drug-resistant influenza viruses and the threat of pandemics in pets and people. Turmeric and curcumin may act in additive or synergistic fashion with anti-infective agents.

The three new chemical entities and ten known curcuminoids isolated from a methanol extract of turmeric strongly inhibited neuraminidases from two influenza viral strains, H1N1 and H9N2. This inhibition was noncompetitive with IC_{50} values ranging from 6.18 ± 0.64 to 40.17 ± 0.79 μg/ml and 3.77 ± 0.75 to 31.82 ± 1.33 μg/ml, respectively. Three compounds (4, 5, and 13) also exhibited significant inhibitory activity against the neuraminidases from novel influenza H1N1 (WT) and oseltamivir-resistant novel H1N1 (H274Y mutant) expressed in 293T cells. These findings suggest that turmeric or its curcuminoids may have preventive and therapeutic potential in the prevention and treatment of diseases caused by influenza viruses.

Recently, Han and his team (2018) demonstrated that daily oral dose of curcumin (100 mg/kg for 7 days) inhibited influenza A virus (IAV) in vitro and reduced the severity of the disease in mice. Curcumin was found to trigger expression of heme oxygenase-1 in vivo and attenuate IAV-induced lung injury. Furthermore, curcumin regulated immune response following IAV infection through inhibiting production of local inflammatory cytokines and NF-κB signaling in macrophages and by enhancing IκBα and AMPK. These data suggest that turmeric or its extract may have promising efficacy in viral pneumonia.

Nonsurgical traumatic wounds lead to bacterial infections. These infections can be a life-threatening medical situation, especially those caused by multidrug-resistant (MDR) bacteria with limited therapeutic options. The antimicrobial activity of polymyxin B and curcumin, alone and in combination, was determined to be effective against MDR bacterial isolates associated with traumatic wound infections. In the presence of curcumin, the minimum inhibitory concentrations of polymyxin B were significantly reduced by a factor of 3- to 10-fold, and it reduced the cytotoxicity of the antibiotic. These findings demonstrate that curcumin exerts antibiotic-sparing effects and this combination acts in a synergistic fashion (Betts et al. 2016). These studies suggest the developing combination formulations containing turmeric or curcumin with antibiotics. This approach may help to reduce the prevalence of multidrug-resistant (MDR) bacteria in hospital settings.

8 Osteoarthritis (OA, Degenerative Joint Disease)

The most common aging-associated diseases in pets and people include dysregulated and persistent chronic immune inflammation, osteoarthritis, rheumatoid arthritis, diabetes, obesity, atherosclerosis, neurodegenerative diseases, hypertension, ocular diseases, osteoporosis, cancer, cardiovascular diseases, and chronic kidney diseases, as well as infections. A vast body of literature on turmeric and its active ingredient, curcumin, shows that they have potential for preventive medicine in aging-associated diseases. Dende et al. (2017) demonstrated that nano-formulated curcumin has a better therapeutic index than the native form of curcumin. Kumar et al. (2018) reviewed the potential role of curcumin and nanocurcumin with improved stability and oral bioavailability and its putative mechanism of action and recent advances in the management and treatment of aging-associated diseases.

Aging horses exhibit chronic, low-grade inflammation, which is often associated with many afflictions including laminitis and osteoarthritis. Nonsteroidal anti-inflammatory drugs (NSAIDs including flunixin, meglumine, and phenylbutazone) are effective in treating acute inflammatory conditions. The chronic long-term treatment with NSAIDs may result in negative side effects. Curcumin (20 μg/ml) was found to inhibit lymphocyte pro-inflammatory cytokine production in aging horse in vitro (Siard et al. 2016). The long-term preventive and therapeutic effect of standardized turmeric, curcumin, and nanocurcumins (targeted drug delivery technologies) on aging-associated diseases in aging pets, horses, and people are warranted.

In dogs, osteoarthritis (OA) is one of the most common causes of lameness. OA is caused by a deterioration of cartilage in the joints. It leads to inflammation, loss of range of motion of the joint, and pain. More than ten million dogs suffer from OA in the USA alone. Repeated traumatic insults to the joints (hip or elbow), joint dysplasia, aging, obesity, and excessive jumping or running or playing or hunting or

other genetic risk factors may result in osteoarthritis in dogs. It is a multifactorial disease of the joints. Akuri and his associates (2017) summarized the pathophysiology of OA. A series of biomechanical and pathophysiological events perpetuate structural degenerative changes in the joint, which often leads to crippling pain, long-term disability, and poor quality of life. Good nutrition, functional foods, caloric restriction, exercise, and herbs (dietary supplements as food) may reduce the need for pain medications (opiates) and anti-inflammatory agents (NSAIDs and cortisone) in pets and people suffering with OA. For preventive strategies, early diagnosis and intervention of OA and comorbidities is absolutely necessary. Besides preventive strategies (proper nutrition, exercise, weight loss, caloric restriction), Ayurvedic herbal supplements in oils (emu oil, coconut oil, hemp oil, or fish oil, omega-3) may offer promise in managing chronic OA.

Analgesics (opiates), NSAIDs, and cortisone are often used in managing OA in aging pets and people. Their clinical utility is limited by adverse effects, low systemic absorption, and high costs. It remains to be discovered if curcumin or turmeric would reduce the need for NSAIDs, cortisone, and opiates in managing OA.

The pathogenesis of osteoarthritis involves processes such as inflammation, osteoclastogenesis, and proteolytic degradation of cartilage. Turmeric and its extracts (curcumin or curcuminoids and non-curcumin turmeric ingredients) have a broad-range pharmacological profile that can modify many aspects of OA and may slow the progression of OA by reducing inflammation and cartilage and bone destruction, especially in the early stages of OA. The vast literature summarized in this review suggest that curcuminoids in turmeric may have potential to benefit patients suffering with osteoarthritis (Akuri et al. 2017). Canine natural osteoarthritis is a realistic model for finding safe and effective doses of dietary supplements as nutraceuticals and/or prescription-grade nutraceuticals for veterinary and human use.

Innes et al. (2003) studied the effect of P54FP (an extract of Indian and Javanese turmeric). Each capsule contained 20 mg curcuminoids (curcumin and desmethoxycurcumin, 50 mg *C. xanthorrhiza* volatile oil, and 150 mg *C. domestica* essential oil), and dogs were treated twice daily for 8 weeks. They reported that this treatment produced a remittance of pain and a recovery of articular movement in dogs.

Zhang et al. (2016) investigated the effect of curcumin using destabilization of medial meniscus (DMM) osteoarthritis mouse model. Immediately after DMM, mice were treated orally with 50 mg/kg curcumin dissolved in corn oil or vehicle (corn oil only) for 8 weeks. The topical application of curcumin nanoparticles or vehicle control (coconut oil) on the skin, within a 5 mm^2 area directly above the DMM operated knee, once daily for 8 weeks. The data obtained in this study demonstrated that oral and topical curcumin administration slows the progression of OA in this post-traumatic osteoarthritis mouse model. This may be translated into an oral human equivalent dose of curcumin of ~4 mg/kg/day for 8 weeks or longer. The delivery of low doses of turmeric or curcuminoids using nanotechnology or target-specific drug delivery may offer affordable, safe, and effective strategies or adjunct therapy for the long-term management and treatment of OA and other chronic inflammatory diseases of the joints, gut, brain, and body.

Jeengar et al. (2016) reported that topical application of curcumin with emu oil inhibited carrageenan-induced rat paw edema and Freund's complete adjuvant-induced arthritis in rats. This combination was effective in bringing significant alterations in the functional, biochemical, histopathologic, and radiologic parameters in rat paw. Their outstanding findings suggest that that topical application of curcumin with emu oil may offer noninvasive intervention for the treatment of inflammatory arthritis in pets and people.

A polar extract of turmeric produced a dose-dependent decrease in monosodium iodoacetate-induced osteoarthritis in rats. This activity was correlated by upregulating type II collagen gene (COL2A1) as well as downregulating MMP-3 and MMP-7. The beneficial effects of polar extract of turmeric may be related to the establishment of equilibrium between catabolism and anabolism of joint cartilage (Murugan et al. 2017; Velusami et al. 2018).

Curcumin (CurcuVetR containing 20% curcuminoids) was found to reduce PMA-induced stimulation of sheep neutrophils and increased spontaneous apoptosis and inhibited both IL8 and Bcl2A1 expression cultured cells within 22 h (Farinacci et al. 2009). They suggested that curcumin may limit the early phases of neutrophil infiltrations, and such an effect may have potential clinical application in the management of ruminant inflammatory disorders. In addition, Colitti et al. (2012) studied the effect of dietary curcumin (CurcuVetR at 4 mg/kg BID for 20 days) on the gene expression of peripheral white blood cells in dogs suffering with OA. They used a 44K oligo microarray technique. This treatment was found to alter the molecular target of inflammatory response. Specific molecular targets of curcumin were inhibition of macrophages proliferation and downregulation of TNFα, TLR4, IL8, IL18, and MAPK14, as well as activation of fibrinolysis. From a mechanistic point of view, these findings suggest good support for OA treatment with low dose of curcumin. They suggest that for drawing a definitive conclusion from this study, a large number of patients (pets and people) are required to validate the use of curcumin for the treatment of OA in dogs.

Recently, Liu et al. (2018a, b) reviewed the vast literature on the efficacy and safety of dietary supplements for patients with osteoarthritis. Seven supplements (pycnogenol, passion fruit peel extract, *Curcuma longa* extract, L-carnitine, *Boswellia serrata* extract, curcumin, and MSM) were found to exert large and clinically significant effects on physical function in the short term in patients living with OA. Del

Grossi Moura et al. (2017) concluded that good-quality clinical research is still lacking and it does not support the use of curcumin and herbal medicines in treating OA. Poor patient adherence and compliance make it very difficult in finding the short-term or long-term efficacy of dietary supplements as with pharmaceutical medications (Liu et al. 2018a, b).

Recently, Haroyan et al. (2018) studied the effects of CuraMed® 500 mg capsules (333 mg curcuminoids) and Curamin® 500 mg capsules (350 mg curcuminoids and 150 mg boswellic acid), taken orally three times a day for 12 weeks, in 201 patients living with OA. This combination appeared to exert synergistic efficacy in 40- to 70-year-old patients suffering with OA. These studies suggest that the long-term use of turmeric and/or its major ingredients as dietary supplement or as foods may slow the progression of OA in pets and people.

9 Pain

Several complementary and integrative approaches including physical activity, exercise, herbs (turmeric, hot peppers, etc.) or their ingredients (curcumin, capsaicin, etc.), vitamin D, omega-3 fatty acids, lipoic acid, acupuncture, yoga, aquatic yoga, meditation, and mindfulness meditation may play important roles in managing chronic pain in people. The high interindividual variability between patients is expected in responses to these pain management modalities (Wojcikowski et al. 2018). The herbs or their extracts (ingredients such as curcuminoids), vitamin D, omega-3 fatty acids, emu oil, and lipoic acid as oral or topical application may be utilized as veterinary nutraceuticals and dietary supplements for chronic pain management.

Curcumin has been reported to exert analgesic effect in animal models and in humans (Cheppudira et al. 2013; Lin et al. 2011; Motaghinejad et al. 2015; Gaffey et al. 2015; Zhu et al. 2014). It may be acting as a transient receptor potential vanilloid-1 (TRPV1) receptor antagonist (Nalli et al. 2017; Zhi et al. 2013; Yeon et al. 2010).

Jhi et al. discovered that curcumin (4 mg/kg/min IV for over 3 min) caused a marked and rapidly reversible inhibition of colorectal distension-induced visceromotor responses (VMRs) in anesthetized rats. In the mouse jejunum, the mesenteric afferent nerve response to ramp distension was attenuated by curcumin (3 and 10 μM). In addition, curcumin (1–30 μM) inhibited the afferent responses to capsaicin in a concentration-dependent manner. Trinitrobenzene sulfonic acid-induced hypersensitivity of jejunal afferents was also attenuated by curcumin. Curcumin potently inhibited capsaicin-induced rise in intracellular calcium and inward currents in mouse or rat dorsal root ganglia (DRG) neurons. These studies demonstrate that curcumin inhibits visceral nociception via antagonizing transient receptor potential vanilloid-1 (TRPV1) receptor TRPV1. This suggests that curcumin or turmeric may help in the treatment of gastrointestinal diseases such as hypersensitive esophagus and heartburn.

Cheppudira et al. (2013) reviewed the effects of curcumin on various pain and wound-healing models in preclinical studies. Patients suffering with peripheral neuropathy (PN) frequently experience sharp spontaneous pain, allodynia, and hyperalgesia. Opioids, anticonvulsants, and tricyclic antidepressants are often used to treat neuropathic pain. These medications are often unsatisfactory because of limited efficacy and adverse side effects. There is unmet medical need for finding novel chemical entities or dietary supplements (nutraceuticals) to manage chronic pain and wound healing in pets and people. The preclinical studies summarized below suggest that turmeric or curcumin may have some potential to treat both pain and wounds. The oral use of curcumin, alone, or as an adjunct therapy, may be useful in the management of postoperative pain and neuropathic pain (Cheppudira et al. 2013; Zhu et al. 2014).

Lin et al. (2011) demonstrated that morphine injections (10 mg/kg, sc) for 7 days produce tolerance in mice. Morphine tolerance is attenuated by co-administration of low-dose curcumin (25 mg/kg, ip) for 7 days. On the other hand, morphine tolerance is aggravated by chronic high-dose curcumin (400 mg/kg/day for 7 days). The acute low-dose curcumin did not enhance morphine's analgesic activity. These observations tend to suggest that high doses of curcumin may be pro-inflammatory and may act by negating other beneficial effects such as inhibiting the expression of antiapoptotic cytokines and neuroprotective factors.

Zhu et al. (2014) summarized the results of many previously published preclinical studies. In a chronic constriction injury (CCI) model of neuropathic pain in rats, single dosing with curcumin did not influence mechanical and thermal hyperalgesia, but repeated curcumin treatment progressively and completely reversed CCI-induced hypersensitivity. The daily curcumin dosing reverts streptozotocin-induced diabetic neuropathy. However, acute curcumin treatment reduces formalin-induced defensive behaviors, visceral pain as measured by acetic acid-induced writhing response, capsaicin-induced thermal hyperalgesia, and reserpine-induced fibromyalgia-like behaviors. They also demonstrated that a surgical incision on the right hind paw of rats induces a sustained mechanical hyperalgesia. It lasted for 5 days. Curcumin (10–40 mg/kg administered by the mouth) apparently in dose-dependent fashion reversed mechanical hyperalgesia in rats. In addition, repeated curcumin treatment facilitated the recovery from surgery. The repeated treatment with curcumin before surgery did not impact the postoperative pain threshold and recovery rate. However, the repeated

treatment with curcumin after surgery reduced postoperative pain threshold and improved recovery rate. The oral use of curcumin, alone or as an adjunct therapy, may be useful in the management of postoperative pain (Zhu et al. 2014).

Motaghinejad et al. (2015) demonstrated that curcumin attenuates morphine withdrawal syndrome. The antinociceptive activity of curcumin in a mouse model of visceral pain is mediated by opioidergic and serotonergic systems. They suggested that curcumin may be effective in attenuating pain during the opioid withdrawal period.

Gaffey et al. (2015) reviewed the effects of curcumin on musculoskeletal pain. Curcuminoids found in turmeric were effective in enhancing wound healing and in the treatment of burn pain and diabetic neuropathic pain. The use of curcuminoids to treat pain associated with knee osteoarthritis showed greater reductions of pain as compared with a placebo, and the efficacy was comparable to the use of ibuprofen. A significant efficacy was found with the use of turmeric extract in combination with other nutraceuticals (devil's claw and bromelain) to treat acute and chronic osteoarthritis pain. A proprietary lecithin formulation of curcumin exerted significant reduction of delayed onset muscle soreness, and the efficacy was comparative to a standard dose of acetaminophen in the treatment of acute pain.

The prolonged use of opioids for the treatment of chronic pain induces opioid-induced hyperalgesia (OIH). It is one of the major clinical problems. A newly developed PLGA-curcumin nano-formulation (PLGA-curcumin) administered intrathecally or orally significantly attenuated hyperalgesia in mice with morphine-induced OIH. This was associated with the suppression of chronic morphine-induced CaMKIIα activation in the superficial laminae of the spinal dorsal horn. These data suggest that PLGA-curcumin may reverse OIH possibly by inhibiting CaMKIIα and its downstream signaling (Hu et al. 2016).

Earlier, Agarwal et al. (2011) reported that curcumin (500 mg capsule every 6 h for 3 weeks) improved postoperative pain and fatigue in patients undergoing postoperative recovery. The effect was more pronounced on days 7 and 14. Furthermore, oral administration of curcumin significantly reduced progression of osteoarthritis (OA) in destabilization of the medial meniscus mouse model. However, it did not influence pain. In addition, topical application of nanoparticles (curcumin) not only reduced pathogenesis of OA but also relieved OA-related pain. Nanoparticles reduced tactile hypersensitivity and improved locomotor behavior. Gera et al. (2017) reviewed the field of curcumin's nanoformulations. These novel formulations of turmeric or curcumin may be an emerging paradigm shift for improved remedial applications in nutraceutical and pharmaceutical settings.

The effect of repeated daily oral doses of curcuminoids (*C. longa* extract, CLE, at 5, 20, or 80 mg/kg/day) was evaluated in hot-plate test in mice. On day 11, all animals were subjected to foot-shock stress triggered by a hyperthermia test and day 12 to a tail suspension test for antidepressants. CLE produced dose-dependent analgesic activity. Interestingly, only low doses of CLE were effective in relieving central pain (Verma et al. 2017).

Bethapudi et al. (2017) evaluated the analgesic effect of turmerosaccharides rich fraction (NR-INF-02) on monosodium iodoacetate-induced OA pain in rat model that mimics human OA. The oral administration of turmerosaccharides rich fraction at 45 and 90 mg/kg was found to decrease OA pain at 1, 3, 6, and 24 h posttest administration on day 5. The effect of turmerosaccharides rich fraction on OA pain was superior to turmerosaccharides less fraction.

Dry socket (alveolar osteitis) is a painful dental condition that happens after a permanent adult tooth extraction when the blood clot at the site of the tooth extraction fails to develop or it dislodges or dissolves before the wound has healed. In a recent study, Lone et al. (2018) demonstrated a significant reduction in mouth pain, inflammation, and discomfort after turmeric dressing in 178 patients diagnosed with dry socket syndrome. Wound healing progressed faster than dressing with ZOE dressing. These studies suggest that the effect of curcumin (curcuminoids) may depend on the time of initiation of treatment, duration of treatment, dose of curcumin, etc. Double-blind placebo-controlled clinical studies are warranted in pets and people suffering with NP, OA, and postsurgical pain.

Curcumin (nanoparticles) may represent a novel topical antimicrobial (antibacterial, antiviral, and antifungal) and wound healing adjuvant for infected burn wounds and other cutaneous and muscle injuries and related pain conditions (Krausz et al. 2015; Gera et al. 2017). Long-term clinical studies are needed to establish analgesic activity of turmeric or curcuminoid nanoparticles (low doses and long duration of treatment in pain-related conditions).

10 Sports Medicine

Traumatic muscular injuries (soft tissue trauma, bruises, and contusions) are too common in dogs and horses. Dietary supplementation with ST or curcumin and other strategies to reduce muscle soreness and to improve muscle (physical) recovery are of great interest to athletes and to people caring for horses and dogs. ST or curcumin may be a suitable alternative to nonsteroidal anti-inflammatory medications for the management of diseases of the musculoskeletal systems such as muscle soreness and OA (Heaton et al. 2017).

Tanabe et al. (2015) studied the effect of 150 mg of curcumin (taken by mouth before and 12 h after each exercise session in a randomized, crossover design study in 14 untrained young men). This treatment reduced maximal voluntary contraction (MVC) torque, and muscles recovered

faster (e.g., 4 days postexercise $-31 \pm 13\%$ vs. $-15 \pm 15\%$); peak serum creatine kinase (CK) activity was less for those treated with curcumin than with placebo ($P < 0.05$). The researchers concluded that theracurmin ingestion may reduce some aspects of muscle damage.

McFarlin et al. (2016) evaluated the effect of curcumin supplementation (Longvida®; 400 mg/day). It reduced CK (a biomarker of muscle injury) by 48% after subjects consumed curcumin for 2 days before and 4 days after a high-intensity muscle damage-inducing protocol. They concluded that consumption of curcumin reduced a biomarker of muscle injury, but not quadriceps muscle soreness or inflammatory biomarkers, during recovery after exercise-induced muscle damage. The observed reduced biomarker of muscle injury may translate to faster recovery and improved functional capacity during subsequent exercise sessions. This conclusion needs to be explored using a large number of sports participants.

Heaton et al. (2017) reviewed nutritional strategies for muscle regeneration, muscle fatigue, physical and immune health, and preparation for subsequent training sessions in sports medicine. They concluded that the anti-inflammatory and anti-oxidative activities of turmeric and its active ingredients suggest that these agents at low appropriate doses may have a role in sports medicine, especially in preventing the consequences of concussions and muscle injuries.

Curcumin or turmeric may provide some recovery benefit or reduced muscle damage during the intense sport activities. Therefore, clinical research using wide doses of ST or curcumin is warranted prior to incorporating supplemental dosages into the athlete's diet or into pet supplements.

11 CNS Effects

Sarker and Franks (2018) reviewed published preclinical and clinical studies related to efficacy of curcumin for age-associated cognitive decline. Ramkumar et al. (2018) summarized the antioxidant, anti-inflammatory, neuroprotective, and antiproliferative activities of curcumin, demethoxycurcumin (DMC), and bisdemethoxycurcumin (BDMC). DMC may have better anticancer and anti-inflammatory activity as compared with curcumin. Recently, DMC (5, 10, and 20 mg/kg, i.p., for 7 days) was shown to abrogate rotenone-induced dopamine depletion and motor deficits by its anti-oxidative and anti-inflammatory properties in parkinsonian rat model. They concluded that DMC may be a promising therapeutic lead for the treatment of neurodegenerative diseases including Parkinson's disease.

12 Diabetes

In developing countries, about 80% of people depend on traditional herbal medicine to meet their healthcare needs. Turmeric has been used for the management of diabetes in Ayurvedic and traditional Chinese medicine. Curcumin reduces glycemia and hyperlipidemia in rodent models of diabetes (Zhang et al. 2013). Dietary curcumin relieves stress in metabolic tissue, leading to improvements in diabetes and associated disease complications in rodent models and in clinical studies. New improved methods of curcumin delivery (nanoparticles and lipid/liposome formulations) may help in cell-directed targeting, and it may offer improved therapeutic outcomes in diabetes (Maradana et al. 2013). In addition, curcumin or curcuminoid supplementation has been reported to be effective in lowering the fasting blood glucose concentrations in people with prediabetes, diabetes, or metabolic syndrome. Curcumin produced significant decrease in HbA_{1c} as compared to placebo. de Meloa concluded that curcumin supplementation may be an adjuvant aid in the management of dysglycemic patients.

Recently, Yang et al. (2018) studied the effects of curcumin on retinal damage in STZ-induced diabetic rats. Curcumin (100 and 200 mg/kg, PO, daily for 16 weeks) was found to reduce diabetes-induced body weight loss, blood glucose, and retinopathy. This activity may be attributed to the hypoglycemic, antioxidant, VEGF-downregulating, and neuroprotection properties of curcumin. They suggested that curcumin may have a potential in the treatment of diabetic retinopathy.

Curcumin suppresses activities of gluconeogenic enzymes and increases glycogen storage in the liver and reduces blood glucose in db/db mice (Fujiwara 2000). Wickenberg demonstrated that 6 g of turmeric taken by mouth increased postprandial insulin levels in healthy subjects. The increased insulin response may be due to the stimulation of β-cell function by curcumin. In addition, oral administration of 10 mg of curcumin (twice a day for 28 days) lowered LDL levels and increased HDL levels in patients with atherosclerosis (Ramirez et al. 2000). In this study, the low dose of curcumin seems to be relevant to what people get while taking low dose of ST or turmeric in the turmeric-consuming nations.

Inhibition of enzymes such as α-amylase could play a key role in the control of diabetes by slowing starch digestion. The inhibitors of pancreatic α-amylase may be of great therapeutic importance in treating diabetes mellitus. Bisdemethoxycurcumin (BDMC) inhibits porcine and human pancreatic α-amylase with an IC_{50} value of 26 and 25 μM, respectively. This may impart antidiabetic activity of turmeric and its metabolites in pets and people. BDMC could be a good drug candidate to reduce postprandial hyperglycemia (Ponnusamy et al. 2012).

Arun and Nalini (2002) studied the effect of turmeric and curcumin on diabetes mellitus in alloxan-induced diabetes in rats. Administration of turmeric or curcumin reduced the blood sugar and glycosylated hemoglobin levels as well as the activity of sorbitol dehydrogenase, which catalyzes the conversion of sorbitol to fructose. Curcumin was more effective than turmeric in attenuating diabetes mellitus-related changes. These results suggest that curcumin may be effective in attenuating diabetes mellitus-related changes.

Normal and diabetic rats were treated with curcumin (90 mg/kg/day) incorporated in yogurt. After 15 days of treatment, the glucose tolerance and the insulin sensitivity were significantly improved in diabetic rats. This improvement may be associated with an increase in the AKT phosphorylation levels and GLUT4 translocation in skeletal muscles. They suggested that curcumin metabolite(s) may be responsible for the antidiabetic activity (Gutierres et al. 2015).

ST, curcumin, and other ingredients present in turmeric and their metabolites may exert antioxidant and anti-inflammatory properties, which may assist in alleviating the complications in diabetes (Gutierres et al. 2015). In addition, curcumin exerts retina-protective effects (Xu et al. 2018; Yang et al. 2018).

13 Metabolic Syndrome

Curcumin is well known to exert an anti-inflammatory effect through downregulation of inflammatory cytokines, transcription factors, protein kinases, and enzymes that promote inflammation and participate in the development of chronic diseases. Such a multitude of effects of curcumin on gut permeability and barrier function, gut-brain axis, genes, epigenetic and molecular targets in mitochondria, and disease-specific target tissues may offer some health benefits in chronic disease states including metabolic syndrome (Shehzad et al. 2017; Ghosh et al. 2018).

Di Pierro et al. (2015) showed the ability of curcumin (complexed with phosphatidylserine in phytosome form or with pure phosphatidylserine) to reduce weight and omental adipose tissue in overweight people with metabolic syndrome in a preliminary clinical study. At the end of the first 30 days of lifestyle intervention, overweight participants were randomly assigned to one of the two groups for the 30-day treatment phase. Twenty-two of the participants were supplemented twice a day for 1 month with a nutritional supplement formulated to be enteric-coated and containing 800 mg/dose/day of *Curcuma longa* extract (95% curcumin), complexed with sunflower phospholipids (20% phosphatidylserine) and blended with 8 mg/dose/day of piperine from *Piper nigrum* extract (Bioperine). After 60 days, the collective weight loss was 6.7%, the BMI decrease was 8.4% with the percentage of fat reduced by more than 9%, and more than 6 cm was lost in waistline and 3 cm lost in hip circumference. These interesting preliminary observations by Di Pierro et al. (2015) suggest that long-term large randomized double-blind placebo-controlled clinical trials using a wide range of doses and formulations of turmeric and curcumin in overweight dogs, cats, and people are needed.

Sohrabi et al. (2018) summarized that pro-inflammatory cytokines such as interleukin-17F (IL-17F) has an association with induction of tissue inflammation and obesity. IL-17F is produced by T-helper (Th) 17 cells, natural killer cells, γδ T cells, CD4+, and CD8+ T cells. High-fructose consumption often increases body weight and serum level of IL-17. Cinnamon and curcumin supplementation decreases IL-17F under the standard diet. Feeding with cinnamon and turmeric (water-soluble extract) caused a decline in body weight but, surprisingly, increased IL-17F in rats on a high-fructose diet (Sohrabi et al. 2018).

A high-fat diet leading to postprandial hyperlipidemia and inflammation appears to be the key etiologic factor contributing to the development of atherosclerosis and subsequent coronary artery disease (Alipour et al. 2007). Acute supplementation with resveratrol (200 mg and curcumin 100 mg) did not modify high-fat diet-induced postprandial circulating inflammatory markers (C-reactive protein, IL-6, IL-8, monocyte chemoattractant protein-1), adhesion molecules (soluble E-selectin, soluble vascular cell adhesion molecule-1 (sVCAM-1)), or soluble intercellular adhesion molecule-1 in older adults with abdominal obesity (Vors et al. 2018). This study suggests that as-needed intake of dietary supplements (PRN basis) may not offer the desired efficacy in most clinical setting in pets and people. Long-term clinical studies are warranted to examine the dose response and newer formulations of curcumin and turmeric, alone or in combination, with other phytonutrients.

Intragastric administration of curcumin at 250 mg/kg daily for 8 weeks was found to decrease the level of free fatty acid and TNF-α in serum of type II DM rats. This treatment also improved the metabolic disorder of glucose and lipid, enhanced the sensitivity to the insulin, and ameliorated the resistance to insulin in rats (Su et al. 2017).

Mantzorou et al. (2018) reviewed recent, well-designed clinical studies and showed that curcumin appears to offer some health benefits against obesity, metabolic syndrome, and diabetes. Furthermore, curcumin may exert a heath beneficial effect in people suffering with arthritis, skin diseases, gut inflammation IBD, UC, cancer, fatty liver disease, depression, and symptoms of premenstrual syndrome. The concrete and precise recommendation cannot be made with respect to dose, formulations, and duration of treatment. They suggested that large- prospective studies are needed using well-designed clinical trials with proper considerations with respect to follow-up times, dosage, formulation, and duration of curcumin or ST supplementation, medication adherence, and patient compliance. Furthermore, a careful consideration

is needed for confounders in each specific chronic disease of pets and people.

Recently, Jin (2018) reviewed curcumin's complex mechanistic approach to drug discovery in metabolic disorders. Curcumin was shown to improve insulin signaling.

Dexamethasone injection induces insulin resistance, while concomitant curcumin gavage improves insulin tolerance (Tian et al. 2015). Insulin resistance attenuating effect of curcumin appears to be dissociated from its anti-inflammatory effect. In the long term, this protective effect may be attributed to its anti-inflammatory, anti-oxidation, and body weight-lowering effects (Jin 2018).

14 Retinopathies

Peddada et al. (2018) reviewed the etiology of eye diseases and mechanism of action for curcumin in eye diseases. They reviewed literature on the potential therapeutic of curcumin in major retinal pathologies. The retina has a rich blood supply and numerous mitochondria and is consistently exposed to pollutants and ultraviolet light (sun exposure, photons of light), which strikes its surface making the retina at high risk of developing ocular pathologies, particularly in aging populations. Oxidative stress and immune inflammatory pathways are well known to contribute to retinal pathology. Curcumin is known to possess anti-inflammatory, antitumor, antioxidant, and VEGF inhibition properties through modulation of numerous biochemical and transcription processes. Curcumin has been reported to slow, and in some cases even reverse, age-related macular degeneration, diabetic retinopathy, retinitis pigmentosa, proliferative vitreoretinopathy, and retinal cancers. The authors concluded that curcumin exerts limited efficacy, mostly in experimental animal studies.

The use of standardized turmeric as orally administered dietary supplement may slow the progression of age-related eye illnesses. Targeted drug delivery of novel formulations of turmeric or curcuminoids in the eye may reduce immune inflammation (HKH syndrome, uveitis). Oral or topical application of turmeric or its curcuminoids may reduce the need for steroids in treating ocular inflammatory conditions in pets and people.

15 Allergy

Allergic asthma is a complex, multifactorial, chronic immune-inflammatory disease of the airways. The allergic responses in the lungs are mediated via multiple complex pathways leading to release of a number of inflammatory mediators (histamine, cytokines, and enzymes) by activated mast cells, eosinophils, and T lymphocytes. Subhashini et al. (2013, 2016) briefly summarized the pathophysiology and treatment strategies of allergic asthma. The available medications (steroids and bronchodilators) are associated with limitations such as serious side effects. The studies summarized here suggest that turmeric and curcumin may have potential therapeutic utility in modulating (preventing and treating) lung allergy (asthma).

Kurup and Barrios (2007) demonstrated that orally administered curcumin suppressed latex allergen-induced Th2 response in mice. The suppression of Th2-mediated allergic responses was evident by reduced IL-4 and IL-13 production, as well as reduced infiltration of eosinophils in the lungs and reduced expression of molecules such as matrix metalloproteinase (MMP-9), thymic stromal lymphopoietin (TSLP), and ornithine aminotransferase (OAT). They concluded that curcumin may have potential therapeutic utility in lung allergy (asthma).

Subhashini et al. (2013) conducted an elegant preclinical study using curcumin in a mouse model of allergic airway inflammation (asthma). Curcumin was dissolved in dimethyl sulfoxide (DMSO) and administered an hour before every ovalbumin challenge (days 19–22). They discovered that intranasal curcumin application (2.5 and 5 mg/kg) was readily absorbed from airway mucosa and was effective in suppressing airway inflammation and allergic asthma.

Intranasal curcumin significantly inhibited leukocytes and eosinophil recruitment to the lungs and decreased eosinophil peroxidase and histamine levels in bronchoalveolar lavage fluid. These observations may suggest that curcumin (intranasal drop or spray) may reduce the need for inhaled or oral steroids and β-agonists by reducing chronic allergic airway inflammation in pets and people. Later these investigators demonstrated that intranasal curcumin (2.5 and 5.0 mg/kg) reduces airway inflammation and bronchoconstriction by modulating cytokine levels (IL-4 and IL-5 and IFN-γ and TNF-α) and sPLA2 activity and by inhibiting PGD2 release and COX-2 expression. Curcumin's anti-allergic (antiasthma) activity is mediated by the suppression of p38 MAPK, ERK 42/44, and JNK54/56 activation during allergic response in the lung. They suggested that curcumin may offer an alternative for the development of nasal formulations and inhalers for asthma management (Subhashini et al. 2016).

Shin et al. (2015) immunized mice with intraperitoneal injection of ovalbumin (OVA) and alum. The OA-sensitized mice were challenged orally with 50 mg OVA and treated with turmeric extract (100 mg/kg) or curcumin (3 mg/kg or 30 mg/kg) for 16 days. Food allergy symptoms were decreased, as were rectal temperature, diarrhea, and anaphylaxis. Turmeric extract significantly decreased food allergy symptoms (decreased rectal temperature and anaphylactic response). However, curcumin treatment showed little improvement. Turmeric extract also inhibited IgE, IgG1, and mMCP-1 levels. Turmeric extract reduced type 2 helper cell (Th2)-related cytokines and enhanced Th1-related cytokines. Turmeric extract ameliorated OVA-induced food

allergy in mice by restoring Th1/Th2 balance. They concluded that turmeric extract significantly ameliorated food allergic symptoms in this mouse model of food allergy through promoting Th1 responses over Th2-dominant immune responses. The orally administered turmeric extract including various components may be useful to ameliorate Th2-mediated allergic disorders such as food allergy, atopic dermatitis, and asthma.

Interleukin-10 (IL-10) is a pleiotropic anti-inflammatory and immunosuppressive cytokine that is produced by innate and adaptive immunity cells including macrophages, dendritic cells, mast cell, natural killer cells, eosinophils, neutrophils, B cells, CD8+ T cells, and TH1, TH2, TH17, and regulatory T cells. CNS, astrocytes, microglia, and neurons are the major sources of IL-10 production. The major source of IL-10 in the periphery is macrophages. Curcumin has been reported to enhance IL_{10} release. This mechanism may play a role in curcumin's actions—managing or treating immune inflammatory conditions of the gut, joints, lungs, heart, blood vessels, and brain (Mollazadeh et al. 2017).

16 Psoriasis

Dendritic cells (antigen-presenting cells) play a critical role for initiating the activation and differentiation of T cells in inflammatory diseases including psoriasis. Diarylheptanoid from *C. kwangsiensis* (DCK) modulated multiple functions of dendritic cells in the immunopathogenesis of psoriasis. Many steps were modified by DCK including antigen uptake, maturation, migration, and pro-inflammatory cytokine production, and it also decreased proliferation and differentiation of Th1 and TH17 and their effector cytokine production. These mechanisms in part may contribute to turmeric efficacy in treating psoriasis (Liu et al. 2018a, b).

17 Kidney Stones

Bas et al. (2009) administered curcumin orally at 75 mg/kg/day dissolved in 10% ethyl alcohol for 6 days (1 day before and 5 days after shock-wave lithotripsy, SWL) in rats. This treatment produced significant differences in histological changes under light microscope ($P < 0.02$) between SWL and control groups on days 7 and 35. This treatment was found to reduce tissue fibrosis, expressions of iNOS and p65, and serum nitric oxide levels and also prevented interstitial, glomerular, tubular epithelial, and endothelial cellular injuries. They suggested that curcumin may be used as a protective anti-oxidative agent to prevent SWL-induced renal injury.

In another study, curcumin (60 mg/kg body weight) was orally administered once daily for 28 days in rats. The calcium and oxalate levels in urine and kidney tissue homogenate were measured, and kidney histopathological examination was performed. Curcumin treatment inhibited the development of kidney stones but failed to reverse the changes caused by the kidney stones (Ghodasara et al. 2010). Herbal extract of turmeric (curcumin), among many other plants' extracts, was found to inhibit struvite formation (Das et al. 2017). Dietary polyphenols, including curcumin, may be promising dietary supplements for the prevention of urolithiasis (Nirumand et al. 2018). This limited research suggests that curcumin may slow the progression of kidney stone formation and fibrosis and may also exert protective effects in the kidneys.

18 Cancer

Cancer is one of the most common causes of death worldwide. There appears to be a link between cancer and diet. The dietary modulation of gut microbiota and miRNAs may play an important role in cancer development and prevalence. Various dietary components such as turmeric (curcumin), fatty acids, resveratrol, and isothiocyanate are often utilized in cancer prevention and treatment; dietary components and fiber serve as probiotics and alter miRNA expression. This vital interaction of functional foods, herbs, fiber, and dietary supplement modulates the vital pathways involved in metastasis, invasion, apoptosis, tumor growth, and cell proliferation (Riaz Rajoka et al. 2018).

Curcumin could enhance the effect of radiation therapy, inhibit angiogenesis and cell proliferation by suppressing NF-κB and its target genes in colon cancer cells, and inhibit cell growth by modulating Akt/mTOR pathways via the downregulation of EGFR. In addition, pancreatic cells treated with curcumin resulted in the downregulation of 18 miRNAs and upregulation of 11 miRNAs; the upregulation of miR-22 led to the suppression of ESR-1 (estrogen receptor 1) and SP1 transcription factors.

Glioma is the most aggressive, lethal, and most prevalent of primary brain tumors. Glioblastoma (glioblastoma multiforme) is a malignant glioma that is almost impossible to cure because of poor drug transportation across the blood-brain barrier (BBB) and the existence of glioma stem cells. Recently, Zhao et al. (2018) discovered that curcumin-loaded RDP-modified liposome (RCL) inhibited glioma cell proliferation and tumor growth using an intracranial glioma mouse model. RCL prolonged the survival time of the glioma-bearing mice from 23 to 33 days; the inhibition mechanism of RCL on glioma cells may involve cell cycle arrest at the S phase and induction of cell apoptosis. This study provides

evidence that nanotechnology (delivery of curcumin to brain cancer cells) has potential for the treatment of human malignant gliomas.

19 Translation from Population Epidemiology and Clinic to Bench

The average estimated daily human consumption of turmeric (ST) in India is approximately 200–600 mg for life (~1–3 mg/kg, BID, TID). This may be translated into curcuminoids estimated daily human dose of ~3–30 mg for life. This consumption of a low dose of turmeric and its active ingredients may explain the low prevalence of Alzheimer's disease (AD) in India (1/4th of USA) and subsequent low cost of healthcare in India. Traditionally, turmeric powder is first seasoned in oil or ghee until it is brown for 1–2 min before it is used in beans, whole grains, rice, or vegetables (personal observation of Indian cooking during childhood). This method may be a reflection of the ancient art of nanoformulation and activation of >235 ingredients in turmeric and other species.

In non-turmeric-consuming nations, including the USA, many people are using higher doses of dietary supplements (curcumin or turmeric) as recommended by the nonscientist and nonbeliever in Ayurveda. High doses may negate its own beneficial health effects. Therefore, there is a need for developing low-dose formulations consisting of turmeric or curcumin/curcuminoids alone or in combination with other herbs or medications. Such novel combinations need to be clinically evaluated in aging dogs, cats, and people suffering with osteoarthritis, pain, and/or mild-to-moderate cognitive deficits (AD) and comorbidities, such as depression. However, such clinical studies require funding and the incentive to pursue this long course for finding an affordable herb for the prevention of chronic inflammatory diseases of the joints, gut, brain, and skin.

As an example, aspirin (81 mg daily for decades) lowers the risk of heart attack and stroke. Looking at aspirin's pharmacology, no one could have predicted such a great clinical outcome. A combination of salicylic acid (and other tricarboxylic acids) and turmeric at low doses used over decades in mid-age may reduce the progression of AD and OA in high-risk populations and pets.

20 Translation: Preclinical to Clinic

Preclinical data from earlier research from UCLA clearly demonstrate that curcumin at low doses has selective distribution in the brain. This finding may have great clinical implications in terms of its nonconventional PK and efficacy. The low (500 ppm) and high (2000 ppm) dose of curcumin in the feed for 6 months increases plasma level in dose-related fashion in mice, yielding 35 ± 14 and 171 ± 19 ng/ml, respectively. However, the brain level of curcumin following low and high dose was 469 ± 22 and 525 ± 125 ng/g, respectively. The brain-to-plasma ratio was 13.4 at low dose and 3 at high dose. Curcumin's half-life is >10 days in the brain and less than 7 h in the plasma (Dr. S. Frautschy, UCLA, personal communication). Long half-life suggests that active ingredients (curcumin and others) will accumulate in the brain and other fatty tissues over days or weeks.

These data may suggest that there is dose-related PK in the plasma, but not in the brain. The pGp transporters in the BBB may be activated by high plasma levels leading to promotion of curcumin's efflux from the brain. This phenomenon may explain the lack of efficacy in clinical trials using "industrial" doses of curcumin. The efficacy of 160 ppm and 500 ppm in feed for 6 months offered almost similar efficacy in a mouse model of Alzheimer's disease (references). Increasing the dose to 2000 or 5000 ppm did not yield better efficacy in mouse model. The translation effort from mice to human has failed in developing curcumin as a potential therapy for Alzheimer's disease. However, the failure in human clinical trials may help us in developing safer and more effective turmeric formulations for veterinary use, particularly for osteoarthritis and cognitive decline (dementia) in aging dogs and cats.

In depression, AD, pain, and ocular inflammation in animal model demonstrate that the low dose of turmeric or curcumin in feed or foods, for the duration of life, may offer an affordable way to reduce the burden of chronic inflammatory disease in aging pets and people. Along with lifestyle changes—exercise and healthy eating—a low dose of turmeric (ST) may reduce the need for opiates and other medications.

21 Gaps and Opportunities

- Recently, Cavaleri (2018) elegantly discussed and summarized the gaps, challenges, and opportunities in making turmeric or its major phytochemicals (e.g., curcumin, curcuminoids) and their active metabolites effective and safe dietary supplements (nutraceuticals) and medications.
- The purity, adulteration, heavy metal lead contamination, stability, and shelf-life of turmeric (standardized turmeric) and its major components in dietary supplements need to be kept forefront in R&D.
- The content of phytochemicals in turmeric may vary drastically from region to region within a country or around the world. This variation may contribute to the differences

in efficacy of many herbal dietary supplements (such as nutraceuticals, including standardized turmeric and its major components). Therefore, standardization of turmeric preparations (combinations) is not only desirable but is warranted.

- Tissue distribution studies (ADME, PK) following chronic administration of therapeutic (low) doses of turmeric (standardized turmeric) and its major components at steady state after 3, 7, or 30 days of dosing in chronic disease states need to be evaluated in dogs, cats, horses, and zoo animals.
- The in vitro and in vivo activities of curcumin in various experimental models so far have not been reproducible in clinical settings. The study of larger populations of cats, dogs, and horses living with natural progression of chronic dysregulated age-related diseases, and a longer duration of treatment with a wide range of doses of ST and varied formulations of curcumin, may offer more reliable data, which may have a better predictive value in the design of long-term clinical trials in pets and people.
- The use of standardized turmeric and its major components, alone or at various doses, in long-term clinical studies is warranted in aging pets and horses.
- The neuroprotective effects of IV, nasal, or oral formulations of ST or curcumin in stroke and concussion and in PTSD victims need to be evaluated.
- Standardized turmeric and its major components may be preferentially distributed to the therapeutic site (immune inflammation) and may serve a preventive (modulatory) role in aging pets and horses.
- Dogs, cats, and horses, as well as zoo animals, suffering with OA, age-related chronic dysregulated immune inflammation, and AD-type conditions are natural disease models. The efficacy of standardized turmeric and its major components needs to be established in aging pets and horses. Such studies are warranted for establishing more reliable and reproducible changes in the biomarkers of diseases over time.
- Long-term studies using turmeric (standardized turmeric) and its major components, alone or in combination, with other nutraceuticals (herbal supplements) and medications in pets, farm, and zoo animals suffering with chronic dysregulated immune inflammatory conditions are warranted. The long-term treatment with turmeric (standardized turmeric) and its major components would produce significant alterations (up- and downregulation of transcription and translation of genes and epigenetic mechanisms, proteins, mRNAs, and enzymes and their receptors and pathways). These kinds of precision clinical medicine studies are still lacking. This therapeutic approach in R&D may offer better and more reliable biomarkers of disease modification in the saliva, lymphocytes, blood, brain, joints, and eyes of dietary supplement-treated and placebo (vehicle)-treated animals and people.
- The aging people and pets at high risk of AD, OA, and other immune inflammatory conditions may be getting little or no amount (and sometimes too much) of standardized turmeric and its major components. Prevention studies are warranted in these high-risk populations to identify appropriate doses and duration of treatment.
- Population-based, broad dose-response, and PK/PD modeling in the presence and absence of medications for pain, depression, and other common illnesses in aging populations is needed. There is potential activation of drug transporters (Pgp) in target tissues such as the BBB and the gastrointestinal system and in joints while using a high dose of turmeric (standardized turmeric) and its major components. This field needs to be further explored.
- The use of turmeric (standardized turmeric) may be an affordable preventive approach for slowing the progression of aging-related chronic diseases. Its lifetime use as a food, rather than a pill or capsule, may be a viable approach to reduce the need for expensive medications with serious side effects in pets and people. Turmeric (standardized turmeric) and its major components may serve as an adjunct therapy in treating diseases of the digestive system, brain, joints, eyes, and body in aging pets and people.
- Nanotechnology and other medication delivery systems in aging pets may offer new approaches in veterinary practice.

22 Concluding Remarks and Future Directions

Turmeric is the dried rhizome (root) of *Curcuma longa* or *Curcuma aromatica* (wild turmeric), *Curcuma wenyujin* (China), and *Curcuma domestica* (Thailand). It is a rhizomatous herbaceous perennial plant belonging to the ginger family, *Zingiberaceae*. More than 133 different species of turmeric have been identified. It is native to the Indian subcontinent and Southeast Asia. Turmeric contains more than 235 active ingredients naturally packed into its root, optimistically in appropriate proportions. These complex phytochemicals (>235), including essential oils, curcuminoids (>89), and turmerosaccharides, as well as curcuminoid-free ingredients, fiber, and their metabolites and products of microbial degradation of standardized turmeric, may act in additive or synergistic fashion as a modulator of dysregulated chronic immune inflammation and pain in disease states in people, pets, and horses.

The average human consumption of turmeric in India is approximately 81 mg twice or three times a day for life (~1–3 mg/kg, BID, TID). This may be translated into curcuminoids' estimated human dose of ~3–15 mg BID, TID for life. The consumption of low dose of turmeric in foods may be responsible for low prevalence of AD in India (one-fourth of USA). A caution must be exercised when statistics and epidemiological data are being considered for possible translation from one culture or nation to others.

One of the Ayurvedic medicine's basic principles is that efficacy cannot be related to plasma level of a major active ingredient in a spice or an herb, and the whole herb is often more efficacious than its individual ingredients. Contrary to this basic principle, R&D teams over the past decades drastically improved the bioavailability of curcumin, turmeric's major active ingredient. Besides improving curcumin's pharmacokinetics, researchers also increased the dose of curcumin in most clinical trials conducted so far without improving its efficacy in cancer and AD.

Standardized turmeric containing curcumin (3, 9, 27, or 81 mg once a day or BID or TID) could achieve steady-state therapeutic level within 3–10 days in the brain of patients or pets suffering with AD or other persistent dysregulated chronic immune inflammatory conditions. This concept may be explored in aging dogs, cats, and horses living with OA and mild dementia. This concept is based on published preclinical studies—similar effects of aspirin and curcumin in vitro and in vivo. Twenty to thirty years ago, it was unforeseeable that 81 mg aspirin could reduce the risk of stroke and heart attack.

Low dose of standardized turmeric (3–4 mg/kg, BID, TID) blended in coconut oil or fish oil may tame age-related, persistent, dysregulated chronic immune inflammation in the brain, eyes, skin, muscles, gut, and other internal organs in pets. It may slow the progression of cognitive decline disorder (CCD) in dogs and cats. Low dose of standardized turmeric may serve as an adjunct therapy in managing many disease states in aging pets—in dogs and cats as well as in horses. The ingredients in turmeric may restore homeostasis in the brain, joints, gut, and other tissues only under disease states acting via many interrelated mechanisms of action.

In non-turmeric-consuming nations, including the USA, many people and pets may be using higher doses of dietary supplements containing curcumin or turmeric. This may negate its own beneficial health effects. Therefore, there is a need for developing low-dose formulations consisting of turmeric or curcumin/curcuminoids, alone or in combination with other herbs or medications. Such novel combinations need to be clinically evaluated in aging dogs, cats, horses, and people suffering with osteoarthritis and/or with mild-to-moderate dementia/Alzheimer's disease and comorbidities.

Standardized turmeric's novel formulations at low doses may exert mild-to-moderate beneficial effects on osteoarthritis, pain, depression, and neurodegenerative diseases. It may reduce the need for analgesics (opiates), antidepressants, anti-AD, steroids, and anticancer medications. The possibility that many active ingredients in turmeric formulations may be acting in additive or synergistic fashion needs to be explored and addressed. The preclinical data support such a concept. Using the latest drug-targeted delivery (nanotechnology) and reliable clinical trial strategies, standardized turmeric may be considered for R&D for the prevention, and possibly for the treatment, of OA and dementia and other aging-related diseases of the eyes, brain, gut, and joints in pets and humans.

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Fenugreek in Health and Disease

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Abstract

Fenugreek is an herb which has been used in traditional medicines for centuries in wound healing, as an aphrodisiac, for promotion of lactation, etc. The consumption of the seeds as a spice results in different medicinal effects such as hypocholesterolemic, antidiabetic, hepatoprotective, antibacterial, anthelmintic, anticancer, and galactogogue. Flavonoids, saponins, pyridine alkaloids, and steroidal sapogenins are some of the phytochemicals present in the plant. The plant is also embraced for its high content of important vitamins, minerals, protein and amino acids, and fibers making it a nutritious fodder for livestock. Extracts of the leaves and seeds of fenugreek are considered safe and are found to have potential therapeutic explicabilities in the treatment and/or management of diabetes, cancer, toxicities, cardiovascular diseases, physical injuries, and hormonal imbalances. The seeds and leaves of this plant are now being incorporated into animal, bird, and fish foods to increase feed intake, to promote weight gain, and to decrease the feed conversion ratio. The addition of fenugreek in the drinking water of poultry reduces stress, and this can be an important strategy to replace the use of antibiotics such as enrofloxacin as an anti-stress agent, and thus the issues of antibiotic residues in meat, as well as widely developing antibiotic resistance, would be less.

Keywords

Nutraceutical · Fenugreek (*Trigonella foenum-graecum*) · Phytochemicals · Sapogenins · Trigonelline · Diosgenin · Galactomannan

1 Introduction

Fenugreek (*Trigonella foenum-graecum* L.) is an annual forage aromatic leguminous herb. The plant was once native to the Mediterranean region, India, China, Northern Africa, and Ukraine but is now cultivated widely in many parts of the world. It is about 30–60 cm tall with smoothed erect untoothed stipulate and 2–2.5-cm-long leaflets. There are 1–2 flowers which are axillary and sessile. Calyx-teeth is linear and pods measure about 5–7.5 cm in length with a long persistent beak often falcate with 10–29 small size seeds without transverse reticulations (Kirtikar and Basu 2002). The seed is 4.01–4.19 mm long, 2.35–2.61 mm wide, and 1.49–1.74 mm thick (Altuntaş et al. 2005). The leaves and seeds of the plant are used as an herb and the seeds are used as a spice. India leads among the countries which produce fenugreek by sharing 70–80% of the global export (Edison 1995).

Fenugreek is also considered as one of the oldest known medicinal plant in recorded history (Lust 1986). This medicinal plant is used in various traditional medicines including Indian Ayurvedic, traditional Chinese medicines, and Egyptian medicine for wound healing, as an aphrodisiac, for promotion of lactation, and many more (Tiran, 2003). Phytochemicals like flavonoids, saponins, steroidal sapogenins, amino acids, and alkaloids are some of the important constituents found in the extracts of leaves, stem, and seeds of *Trigonella foenum-graecum* L. (fenugreek). The consumption of the seeds as a spice results in different medicinal effects such as hypocholesterolemic (Mathern et al. 2009), antidiabetic (Ajabnoor and Tilmisany 1988), hepatoprotective (Pribac et al. 2009), antibacterial (Sharma

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R. C. Gupta et al. (eds.), *Nutraceuticals in Veterinary Medicine*, https://doi.org/10.1007/978-3-030-04624-8_2

et al. 2017), anthelmintic (Khadse and Kakde 2010), anticancer (Alsemari et al. 2014), and galactogogue (Betty 2008). These phytochemicals also now serve as raw materials for the manufacture of various therapeutic and hormonal drugs (Priya et al. 2011). Fenugreek is also a good source of dietary fiber where the proportions of soluble and insoluble fibers present in its seeds are 13% and 32%, respectively (Roberts 2011).

The antidiabetic and hypocholesterolemic effects of fenugreek are attributed to multiple components. However, these effects, especially the hypoglycemic effect, may partly be secondary to the fiber content which is known to affect gastric emptying and subsequently decreasing the postprandial glucose level in blood (Srinivasan 2006; Benzie and Wachtel-Galor 2011).

Scientific Classifications

Kingdom:	Plantae
Subkingdom:	Tracheobionta
Super-kingdom:	Spermatophyta
Division:	Magnoliophyta
Class:	Magnoliopsida
Subclass:	Rosidae
Order:	Fabales
Family:	Leguminosae/Fabaceae
Genus:	*Trigonella*
Species:	*T. foenum-graecum* (Kirtikar and Basu 2003; Dymock et al. 2005)

2 Phytoconstituents

2.1 Leaves

The green leaves of fenugreek contain numerous phytochemicals, including various nutrients and vitamins. The fresh leaves are used as vegetables in diets mainly for their rich content of vitamins and minerals, and they have also been used as green fodder for livestock. The moisture, nutrient, and mineral contents in fenugreek leaves are shown in Table 1. Ascorbic acid and β-carotene contents in the fresh leaves of fenugreek are about 220.97 mg and 19 mg/100 g of leaves, respectively (Yadav and Sehgal 1997). Minerals like zinc, iron, phosphorous, calcium, etc. and vitamins like riboflavin, carotene, thiamine, niacin, vitamin C, etc. are also present in the leaves (Rao 2003) (Table 2).

2.2 Seeds

Phytochemical constituents in the seeds, husk, and cotyledons of fenugreek differ. The endosperm shows the highest saponin and protein content, while the husk shows a higher polyphenols content. The mature seeds contain about 0.1–1.5% of diosgenin (a steroidal sapogenin) and are extracted commercially (Saxena et al. 2013). Volatile and fixed oils are also present in fenugreek seeds in small amounts (Sowmya and Rajyalakshmi 1999). Among multiple flavonoid glycosides isolated from the seeds of fenugreek, isoorientin has been found in significant amount (Luan et al. 2018). Tables 3 and 4 show the list of chemicals present in fenugreek seeds.

Other constituents of the seed extracts include fibers, gum and neutral detergent fiber (Yadav et al. 2011), and lipids, triacylglycerols, diacylglycerols, monoacylglycerols, phosphatidylcholine, phosphatidylethanolamine, phosphatidylinositol, free fatty acids (Chatterjee et al. 2010), and many others. The chemical structures of some of the bioactive phytochemicals present in fenugreek are shown in Figs. 1 and 2.

Table 1 Nutrient content of fenugreek leaves (Rao 2003)

Moisture	86.1%
Protein	4.4%
Fat	0.9%
Minerals	1.5%
Fiber	1.1%
Carbohydrates	6%

Table 2 Saponins, pyridine alkaloids, and steroidal sapogenins in fenugreek seeds

Flavonoids	Vitexin
	Tricin
	Naringenin
	Quercetin
	Luteolin
Saponins	Graecunins
	Fenugrin B
	Fenugreekine
	Trigofoenosides A–G
Pyridine alkaloids	Trimethylamine
	Neurin
	Choline
	Gentianine
	Carpaine
	Betain
	Trigonelline
Steroidal sapogenins	Yamogenins
	Diosgenin
	Smilagenin
	Sarasapogenin
	Trigogenin
	Neotigogenin
	Gitogenin
	Yuccagenin
	Saponaretin

Source: Review article of Khorshidian et al. (2016)

Table 3 Proteins and amino acids, vitamins, and minerals in fenugreek seeds

Chemical composition		Nutrient value (per 100 g)
Protein and amino acids	Globulin	–
	Albumin	–
	Lecithin	Totally 25.4 g
	Histidine	–
	Lysine	–
	4-Hydroxyisoleucine	–
Vitamins	Vitamin A	1040 IU
	Vitamin C	12 mg
	Niacin	6 mg
	Pyridoxine	0.6 mg
	Thiamine	0.41 mg
	Riboflavin	0.36 mg
	Nicotinic acid	1.1 mg
	Folate	57 μg
Minerals	Calcium	176 mg
	Iron	33.5 mg
	Zinc	2.5 mg
	Phosphorus	296 mg
	Magnesium	191 mg
	Manganese	1.22 mg
	Selenium	6.3 μg

Source: Review article of Khorshidian et al. (2016)

Table 4 Chemical Composition of fenugreek (FK) seed (AOAC 1990)

Items	Percentage
Moisture	7.15
Dry matter	92.85
Organic matter	33.03
Crude protein	16.51
Ether extract	9.49
Total ash	7.15
NFE	33.82
ME(kcal/kg)	38.52

3 Uses of Fenugreek

Food is a major determinant for the health of animals including birds and fish. It not only helps in maintaining normal body functioning and metabolic status, but also the various constituents in feeds such as antioxidants, minerals, vitamins, fibers, etc. aid in disease prevention.

3.1 Ethnohistorical Uses of Fenugreek

Fenugreek is one of the oldest medicinal plants used for many ailments. The plant was traditionally used as galactogogue in Indian subcontinent (Betty 2008), as an analgesic in labor/delivery in ancient Rome, as a health tonic, and in treatment of edema and leg weakness in traditional Chinese medicine (Yoshikawa et al. 2000). The leaves and seeds are used as vegetable or green fodder for livestock (Ahmad et al. 2016) and as a spice (Wani and Kumar 2016), respectively, in many parts of the world.

3.2 Fenugreek Uses in Animal Health

Extracts of the seeds, shoots, roots, and leaves of fenugreek have shown multiple pharmacological properties, such as antimicrobial (Wagh et al. 2007; Norziah et al. 2015; Adil et al. 2015), antifungal (Haouala et al. 2008), anticancer (Raju et al. 2004; Shabbeer et al. 2009; Alsemari et al. 2014), hepatoprotective (Pribac et al. 2009), antidepressant (Kalshetti et al. 2015), antidiabetic (Sauvaire et al. 1998; Naicker et al. 2016), antiulcerogenic (Pandian et al. 2002), hypotensive (Moradi and Moradi 2013), anti-inflammatory, antipyretic, and analgesic (Malviya et al. 2010).

3.2.1 Diabetes

Diabetes, a group of metabolic disorders, is not limited to humans. Many animals, including pets, birds, and wild animals, also suffer diabetes naturally or by other influences. The hypoglycemic effect of fenugreek seeds in the human patient, as well as in chemically induced diabetic animals (rats, dog), has been described by many researchers. Decoction and ethanol extract of fenugreek seeds produced anti-hypoglycemic effects in alloxanized mice in a dose-dependent manner (Ajabnoor and Tilmisany 1988). This effect on blood glucose level in part has been attributed to the presence of steroids, saponins, alkaloids, and fiber content in the seeds. Soluble dietary fiber (SDF)—galactomannan of the plant—can improve glucose homeostasis in type I and type II diabetes by delaying carbohydrate digestion and absorption and enhancing insulin action. The viscous and gel-forming properties of SDF prevent macronutrients absorption, reduce postprandial glucose response, and beneficially affect certain blood lipids (Ou et al. 2001). Trigonelline, a pyridine alkaloid, apart from its antioxidative effects, can alter the activities of enzymes involved in glucose metabolism, β-cell regeneration, and insulin secretion (Zhou et al. 2012). The treatment of alloxan-induced diabetic rats with fenugreek seed powder modulated key enzymes like glycolytic, gluconeogenic, and NADH-linked lipogenic enzymes in the liver and kidney necessary for normalizing glucose level (Raju et al. 2001). Furostanol, a saponin constituent of fenugreek extract, increases feed intake and weight gain in diabetic rats (Petit et al. 1995). Saponins also modulate the disaccharidase and glycogen enzyme activities in the intestine, which results in increased hepatic glycogen content and suppression of blood glucose level. Diosgenin, a

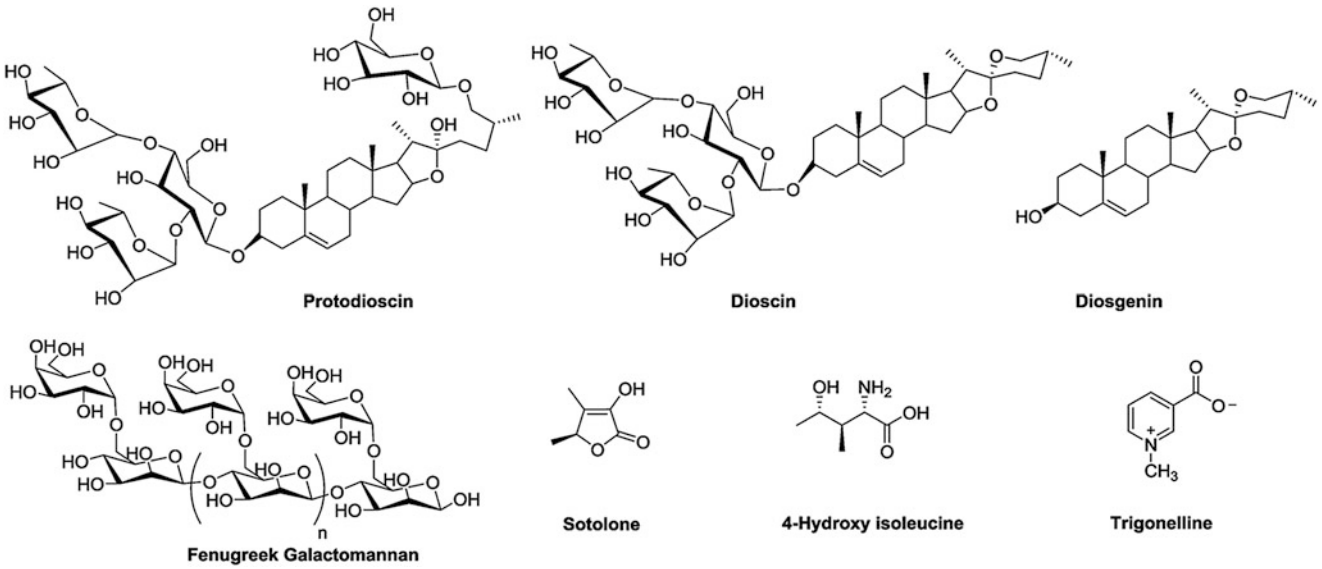

Fig. 1 Structures of some of the important phytochemicals present in fenugreek. Source: Review article of Venkata et al. (2017)

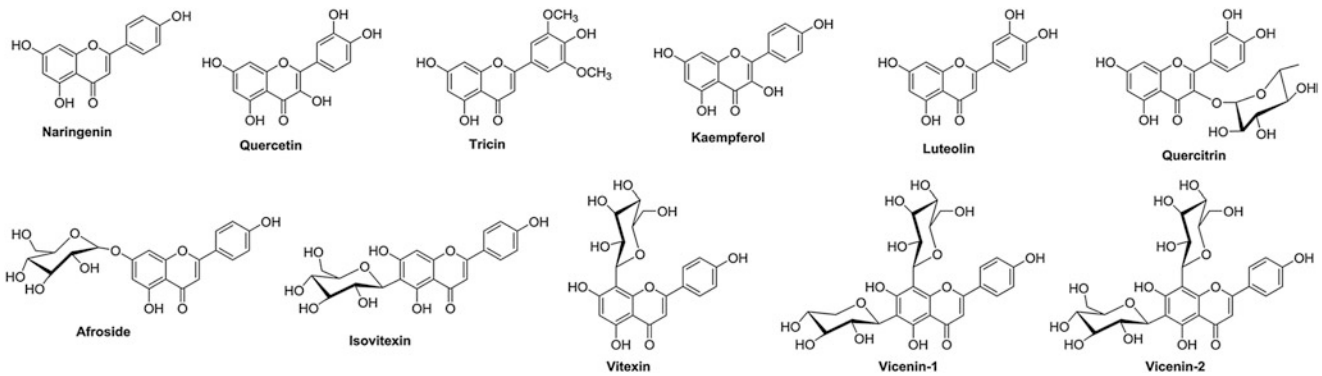

Fig. 2 Flavonoids and their derivatives present in fenugreek. Source: Review article of Venkata et al. (2017)

bioactive steroidal sapogenin belonging to the triterpene group, is a product of the hydrolysis of saponins. Diosgenin content in fenugreek seeds is higher than in its aerial parts (Dangi et al. 2014). This compound is a precursor for several hormones and is extracted commercially for producing sex hormones and other important steroidal drugs. The antidiabetic potential of diosgenin may be attributed to its multiple effects including renewal of pancreatic β-cells, stimulation of insulin secretion, antioxidative effects, stimulation of differentiation of adipocytes, and enhancement of insulin-dependent glucose uptake (Son et al. 2007; Uemura et al. 2010; Kalailingam et al. 2014). Diosgenin also exhibits renal protection in diabetic rats through its anti-inflammatory and antioxidative actions (Kanchan et al. 2016). Subsequent reduction of lipid peroxidation in the liver of diabetic rats after treating with fenugreek has also been attributed to its antioxidative actions (Jin et al. 2014). A nonprotein amino acid, 4-hydroxyisoleucine (4-HIL), is one of the extensively studied phytochemicals present in fenugreek which has insulin-like action and can stimulate insulin production, thereby controlling blood sugar levels in diabetic patient as well as in vitro studies (Gupta et al. 2001). This unusual amino acid is even safer and more effective than many of the current medications available for the treatment of type 2 diabetes mellitus (Zafar and Gao 2016).

The neurological consequences associated with this metabolic disease in the CNS are now receiving considerable attention (Kamboj et al. 2009). Oxidative stress has been implicated in the pathogenesis of many neurodegenerative diseases (Chen et al. 2012). Hyperglycemia generates many free radicals in the diabetic patient, ultimately leading to increased damage of plasma membranes and simultaneous reduction in antioxidant levels (Preet et al. 2005). There is also an increase in Ca^{2+} levels concomitantly with free radicals, which actually correlates to the increase in cellular lipid peroxidation of the synaptosomal membrane and

inhibition of Ca^{2+}ATPase activity (Pekiner et al. 2005; Kamboj et al. 2009). Administration of fenugreek also reduces some of the aberrations that occur in the brain during diabetes, mainly due to its antioxidative activities and neuroprotective effects.

3.2.2 Cholesterol Lowering and Cardiovascular Protection

Cardiovascular diseases (CVD) are the leading cause of human death and morbidity globally (Mendis et al. 2011). Proper management of the cholesterol level in the hypercholesterolemic patient is essential to prevent cardiovascular diseases. Statins alone or in combination with some other drugs are commonly used for controlling increased cholesterol levels. Hundreds of plant-based medicines are also used either singly or in combinations in traditional systems of medicine for the treatment of coronary heart diseases (Mahady 2009). Fenugreek seeds lower serum cholesterol, triglyceride, and low-density lipoprotein in hypercholesterolemic and diabetic patients (Sharma et al. 1996; Mathern et al. 2009) and animals (Sauvaire et al. 1991; Boban et al. 2009). Administration of fenugreek in obsessed rats also reduces triglyceride accumulation in liver while increasing the fecal bile and cholesterol excretion (Rashmi and Rahul 2011). This increased excretion of bile and cholesterol is considered to be a consequence of the reaction between bile acid and fenugreek-derived saponins in the gut causing formation of large micelles which cannot be absorbed easily from the gut (Olaiya and Soetan 2014). The cholesterol-lowering potential of fenugreek is also attributed to its high fiber content. Soluble fiber from fenugreek seemed to reduce reabsorption of bile constituents in the small intestine through binding cholesterol and bile acids and disruption in the enterohepatic cycle in vivo. This enhances utilization of cholesterol in bile acid biosynthesis, subsequently reducing its level (Muraki et al. 2011).

3.2.3 Cancer

Many constituents in fenugreek have shown to exhibit antitumor or anticancer activities in vivo and in vitro. Some of these important constituents include diosgenin (Raju et al. 2004), trigonelline (Bhalke et al. 2009), and flavonoids (Ahmed et al. 2017). Phytoestrogens and saponins present in fenugreek extracts are found to possess anticancer activity in vitro (Raju et al. 2004). Saponins in the extracts not only selectively inhibit cell division in tumor cells but also can initiate apoptosis of the cells (Francis et al. 2002). Diosgenin, a steroidal saponin, has shown antitumorigenic activities in colorectal cancer, osteosarcoma, hepatocellular carcinoma, breast cancer, and leukemia. The effects of diosgenin are mediated through various pathways such as the STAT pathway (Li et al. 2010), activation of p53 and caspase-3 (Liu et al. 2005), and the induction of the tumor necrosis factor-related *apoptosis*-inducing ligand (TRAIL) death receptor DR5 (Lepage et al. 2011). A study in rats revealed the anticancer activity of diosgenin from its ability to inhibit the formation of aberrant crypt foci (ACF), which are clusters of abnormal tube-like glands in the lining of the colon and rectum and can be observed as preneoplastic lesion (Raju et al. 2004). Diosgenin suppressed the expression of bcl-2, a proapoptotic protein, and increased the expression of caspase-3, an anti-apoptotic protein (Raju et al. 2004). Cytokine TNF-α is known to promote cell proliferation, an event common in the initiation and promotion of malignant disease. Diosgenin may also act against bone cancer through the inhibition of TNF-α, thus suppressing proliferation and development of bone cells (Shishodia and Aggarwal 2006). The effectiveness of the fenugreek plant was also seen in colon cancer through the modulation of β-glucuronidase and mucinase activities (Devasena and Menon 2003). Limiting the activities of β-glucuronidase and mucinase in the colonic mucosa may enhance the effectiveness of chemotherapy in colon cancer. The increased activities of β-glucuronidase promote the release of free carcinogens from carcinogen-glucuronide conjugates by enhancing the process of hydrolysis within the colonic lumen, and mucinase assists by hydrolyzing the protective mucin in the gut (Beaud et al. 2005; Booupathy et al. 2016). Fenugreek can decrease the activities of both β-glucuronidase and mucinase in colonic mucosa and may subsequently prevent free carcinogens from acting on the colonocytes (Devasena and Menon 2003).

3.2.4 Antibacterial and Antifungal Effects

The antibacterial and antifungal activities of fenugreek have been reported by many investigators in recent years. The examination of methanol, acetone, and aqueous extracts of fenugreek leaves, seeds, and stems against *E. coli* and *Staphylococcus* isolated from spoiled cabbage revealed the antibacterial property of the herb. The methanol extract of the leaves demonstrated the highest effect, while the aqueous extracts showed the least (Sharma et al. 2017). Mercan et al. (2007) reported an interesting finding that honey samples with the highest antibacterial activity against several bacteria such as *Staphylococcus aureus*, *Escherichia coli*, and *Pseudomonas aeruginosa* displayed maximum pollens from fenugreek as compared to other plants. The extracts were also effective against *Helicobacter pylori* (Randhir et al. 2004).

Fenugreek extracts are also effective against several fungal strains including *Fusarium graminearum*, *Rhizoctonia solani*, *Botrytis cinerea*, *Alternaria* sp., and *Pythium aphanidermatum* (Haouala et al. 2008). However, the potency of the extracts varies with different parts of the fenugreek plant and also the species of fungus. Defensins are small cysteine-rich cationic proteins and function as host defense peptides. A defensin-like peptide, Tf-AFP, with a molecular mass of 10.3 kDa is present in fenugreek and was

isolated from fenugreek seeds by Oddepally and Guruprasad (2015). These defensins are active against bacteria, fungi, and many viruses (Kagan et al. 1990).

3.2.5 Cutaneous Wound Healing

Many herb and spice extracts contain numerous constituents which enhance cutaneous wound healing. Antioxidant activity is one of the major effects of such bioactive constituents which can eventually reduce excessive or chronic inflammation during injury and subsequently promote wound healing. Topical application of 10 % fenugreek seed ointment promoted formation of cellular fibrous connective tissue, granulation tissue, and early maturation of fibrous connective tissues and thus enhanced wound healing in rabbits (Muhammed and Salih 2012). In another study in rats, topical or oral administration of the fenugreek seed suspension quickened contraction and epithelization of the cutaneous wound (Sumitra et al. 2000). Apart from its antioxidative actions, several other constituents present in the extracts are capable of modulating the different phases of healing, which include inflammation, cell proliferation and migration, angiogenesis, and maturation. Antioxidative and antibacterial activities exerted by several constituents of fenugreek extracts are considered important factors augmenting the healing processes (Muhammed and Salih 2012; Ktari et al. 2017). Moreover, fatty acids present in fenugreek seed help in building collagen and consequently promote wound healing and maintenance of skin elasticity (Dixit et al. 2005).

3.2.6 Toxicity Amelioration

Fenugreek is hepatoprotective (Kaviarasan and Anuradha 2007). The antioxidative (Reddy and Srinivasan 2011), anti-radical, and iron metabolism normalizing effect of fenugreek are thought to impart hepatoprotection (Kaviarasan et al. 2007). Incorporation of fenugreek seeds powder (FSP) (5%) in pelleted diet ameliorated chronic liver injury induced by $AlCl_3$ in Wistar rats (Belaïd-Nouira et al. 2013a). The altered liver enzymes and protein levels returned to normal after feeding FSP. Moreover, fenugreek could reduce nephrotoxicity (Belaïd-Nouira et al. 2013b). Fenugreek has shown effectiveness in preventing liver cell necrosis in primary rat hepatocytes culture against *N*-methyl- *N*-nitro-*N*-nitrosoguanidine (MNNG) toxicity in vitro (Khader et al. 2007). Furthermore, the plant has potential for initiating regeneration of hepatocytes during injury. Kaviarasan et al. (2006) reported that in ethanol-induced liver damage, protection of hepatocyte structure and function by fenugreek seed aqueous extract occurred in a dose-dependent manner. Ethanolic extract of fenugreek seed reduced dimethoate (an OP compound)-induced pancreatic damage (Mesallam et al. 2018). Nevertheless, fenugreek extracts were found to potentiate apoptosis of cells induced by radiation, and this cytotoxicity was pronounced in T cells of humans. The cytotoxic potentiative effect of this extract can be of great use in cancer research and treatment by reducing unwanted side effects in those patients who are more sensitive to radiation. However, more in vivo and in vitro studies are needed to support these findings for final validation of effects (Tavakoli et al. 2015).

3.2.7 Gastroprotection

The aqueous extract of fenugreek seeds and a gel fraction isolated from the seeds have ulcer protective potential when compared with omeprazole on ethanol-induced gastric ulcer in experimental rats (Pandian et al. 2002). A similar result was observed on aspirin-induced gastric ulcer in rats using ranitidine as the standard drug (Thirunavukkarasu and Anuradha 2007). This cytoprotective effect was not only due to anti-secretory action of the seed but also attributed to the effects on mucosal glycoproteins. Development of a mucin-like gel layer of galactomannan on the surface of the gastric mucosa forms a barrier, protecting the mucosa from ulcerogenic agents as well as from the gastric juice pepsin in the stomach (Madar and Shomer 1990). Moreover, the antioxidative actions of the seed extract may also contribute to diminishing mucosal injury (Narender et al. 2006). Figer et al. (2017) demonstrated that fenugreek aqueous extract at different concentrations significantly inhibited cell death better than misoprostol sodium against ethanol-induced damage in human gastric carcinoma epithelial cell line in vitro. Higher concentrations beyond 5.0 μg/ml resulted in a decrease in activity. In silico analysis revealed a remarkable degree of interaction of flavonoid constituents with H^+/K^+ ATPase receptor binding sites demonstrating the promising therapeutic potential of fenugreek seed extract as gastroprotective (Figer et al. 2017).

3.2.8 Other Benefits of Fenugreek

Apart from the uses discussed above, fenugreek is well known for its multiple pharmacological actions. Changes in hepatic lipid metabolism can result in development of chronic liver disease (Corey and Cohen 2015). Fenugreek can lower hepatic lipids in the body because of its potential to modify the activities of several enzymes including enzymes related to glucose and lipid metabolism (Madar and Shomer 1990).

Fenugreek is anthelmintic as it causes the evacuation of parasitic intestinal worms. Alcoholic extract of fenugreek seeds has shown anthelmintic activity against earth worm comparable to albendazole in vitro (Khadse and Kakde 2010). However, the aqueous extract was less potent than albendazole (Buchineni and Kondaveti 2016). The effectiveness of the extracts is also reported against *Hymenolepis nana*, *Syphacia obvelata*, and *Moniezia expansa* (Ghafagaai et al. 1980).

Fenugreek is a potent immunostimulant which can stimulate both humoral (Tripathi et al. 2012) and cell-mediated