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TURMERIC (*CURCUMA LONGA* LINN.); A PANACEA FOR HUMAN HEALTH

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ABSTRACT: In medical science, “A panacea is a universal remedy for all kinds of diseases of human being”. “It has the ability to cure all diseases.” Turmeric, botanically identified as *Curcuma longa* Linn. (Zingiberaceae family) is an Indian Ayurvedic drug which has been used in medicine, food, cosmetic and dye ever since the time of the Vedas. It is a plant native to India and has been used for the treatment of a number of diseases in Ayurvedic literature. The rhizome of the plant is used for medicine and food either in the fresh form or in dried form. In Ayurveda, the drug is effective for the treatment of indigestion, constipation, haemorrhoids, helminthes, jaundice and hepatitis, respiratory diseases like asthma, bronchitis, chest allergy, rhinitis, sinusitis, all kinds of poly urea including diabetes, joint pain and swellings, skin diseases and soon. The list of indications of Turmeric is very high as per classical Ayurvedic literature. Interestingly the drug has also been extensively studied on the basis of modern scientific parameters on a number of human pathologies mainly related to inflammation, allergy, autoimmunity, tumor formation and free radical induced damages. This review attempts to compile and present all these medicinal efficacies of Turmeric on the basis of published classical and modern literature in such a way that justifies the fact that “medicinal efficacy of Turmeric is nothing less than the efficacy of a panacea”. Details will be discussed in the manuscript.

INTRODUCTION: As per Cambridge Dictionary, the meaning of Panacea is “something that will solve all problems or cure all illnesses”¹. According to Mariam Webster dictionary the meaning of panacea is “a remedy for all ills or difficulties: cure-all”. As per Taber’s medical dictionary, the meaning of the word panacea is “A hypothetical or ideal remedy for all ills; a cure-all”.

It has been derived from the Latin word panacēa and its root in the Greek word panákeia (from the word panakēs, meaning “all-healing”) were applied especially to flowering herbs of the genus *Opopanax* of the umbelliferae/apiaceae family used to treat various ailments².

It can be regarded as a universal remedy for all diseases and illness. That means a drug or a substance which can cure all kinds of diseases is called as a panacea. Does such a substance really exist on this planet?. The answer will be either Yes or No. Although practically it may not be true to the fullest extent, partially it can be true when it comes to some specific Ayurvedic medicinal plants which have a diverse area of therapeutic actions.

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There exists a similar concept in Ayurveda that is called as Rasayana (rejuvenation), a branch of Ayurveda, which cures all kinds of physical and mental illness along with providing freedom from infectious diseases thus prolonging the lifespan. These drugs can be used in a wide number of physical and mental diseases on the basis of their description in Ayurvedic system of medicine³. Turmeric, commonly called as Haldi, Haridra, Haldu, Manjal in Indian languages and botanically identified as the golden color rhizome of *Curcuma longa* Linn. Syn. *Curcuma domestica* Valetton. (Zingiberaceae family) partially fulfills these criteria although it is not mentioned under the context of Rasayana. The rhizome is typically golden yellow in color and is used for medicinal purposes both in dried and fresh form thus being reputed as the “Golden saffron”. The drug has been indicated in a diverse range of diseases of almost all physiological systems of the human body in Ayurvedic literature. Keeping in view its diverse therapeutic actions, a review has been carried out on existing literature on Turmeric from Ayurveda and from the current contemporary modern medico-bioscientific literature which justifies it to be a true panacea or a partial panacea⁴.

Turmeric has been a native plant of India since time of the Vedas and has been subsequently transmitted to other parts of the world either by commerce or by transmigration of people during various parts of human history. In India it has been used as a traditional medicine, cosmetic, food, food additive, spice, coloring agent and a religious material. Every house hold in India has a stock of Turmeric either in the raw form or in the powder form. It is used in medicine for the treatment of diseases of human being, animals and plants. In Ayurvedic medicine, it is used for the treatment of jaundice, skin infections, respiratory diseases, allergic conditions, wounds and ulcers, inflammation, diabetes, respiratory ailments, obesity, body pain, fever, obesity, heart diseases, urinary troubles, digestive troubles etc.^{4,5}. It is also used as an important medicinal plant in the Indian Siddha, Unani and Traditional Chinese System of Medicine⁶.

Distribution: *Curcuma longa* Linn is native to India and is cultivated all over India. Almost all the states of India cultivate Turmeric to some extent

although Maharashtra is the largest producer followed by Telangana and Tamil Nadu. The states of Telangana, Maharashtra, Tamil Nadu and Andhra Pradesh together contribute 63.4% of India's turmeric production.

Other important turmeric producers are Odisha, Karnataka, West Bengal, Gujrat, Meghalaya and Assam. Interestingly India is the largest consumer, producer and exporter of Turmeric in the world. Turmeric has not been found in the wild⁶.

Taxonomical classification: *Curcuma longa* Linn belongs to the Kingdom-Plantae, Subkingdom-Tracheobionta, Superdivision-Spermatophyta, Division/phylum-Magnoliophyta (angiospermae), Class liliopsidae (monocotyledons), subclass-Zingiberidae, Order-Zingiberales, Family-Zingiberaceae, Genus-Curcuma, Species *Curcuma longa* Linn.⁷.

Sanskrit synonyms: At least 84 synonyms are mentioned in Sanskrit literature for Turmeric. Out of them Haladi, Haridra, Kanchani, Pitaa (due to golden yellow in color), Nishakhya, Nisha, Rajani (all are synonyms of night), Varavarnini, Varnyaa (gives complexion to the skin), Krimighni (anti helminthic), Visaghni (effective in treating poison), Yoshitpriya (used as a cosmetic by Indian women for applying over skin), Hatta Vilasini (adds beauty to the market due its golden yellow color), Mehaghni (effective in polyurea) are important. The synonyms of Turmeric are based upon either its therapeutic actions or its pharmacological actions, or its color and external features or its use for cosmetic purposes or various colloquial features associated with it^{4,5}.

Local and vernacular names: Various local and vernacular names of turmeric are Haldi, Halad, Hardi in Hindi, Hardakh in Punjabi, Halud in Bengali, Halad in Marathi, Haldar in Gujrati, Manjal, Makhali in Tamil, Manjal, Kooneit in Malayalam, Pasupu in Telugu, Zirshud, Urukussaphar in Arabic, Arasina in Kannad, Lidar in Kshmiri, Halad in Konkani, Tanum in Burmese, Jardachobah, Serd-Chubah in Persian, Hardul in Sindhi, Curcuma long in French and Turmeric, Indian saffron in English languages. In Latin language, it is called in the name of *Curcuma longa*^{4,5}.

MORPHOLOGY: Turmeric is a tall perennial monocot herbaceous plant that reaches up to 2 meters in height. Root stalk- are large, rhizomatous and centrally ovoid with lateral cylindrical tubers with dark orange-yellow color inside arising from the ovoid rhizome. Leaves are very large, in tufts, upto- 1.2 meters or more in length including the petiole which is as long as the leaf blade, oblong, lanceolate, tapering to the base and narrowing at the apex and has a width of 38 to 45 cm. The leaves are simple and alternate and arranged in two rows.

Inflorescence-In autumnal spikes, 10, 15 cm long, peduncle -15 cm or more, concealed by the sheathing petiole, flowering bracts are pale green in color. Flowers are pale yellow and as long as bracts. Calyx has three sepals and is of 0.8 to 1.2 cm long, fused and white, with fluffy hairs. Corolla has three bright yellow petals which are fused and is funnel shaped and is up to 3 cm long. Upper half of corolla is pinkish white. Stamens are modified into staminodes. Carpels are three in number. The fruit is a capsule and opens with three compartments. Flowering and fruiting season- is autumn (August, September)^{8,9}.

Useful part/Rhizome Rhizomes occur in two forms. Primary central rhizome is round and the lateral rhizome is long and cylindrical. The long Turmeric is cylindrical in shape and is up to 7 cm long and up to 1.5 cm in width with a yellowish brown external surface with small round root scars. The round Turmeric is ovate, oblong or conical in shape, 4-8 cm in length and is 2-3 cm in diameter. Transverse section of both, show a waxy surface of deep orange color. The central pith is twice as broad as cortex. It has characteristic aromatic odor and bitter taste^{8,9}.

Curing of Turmeric: A specific treatment which involves boiling and drying under sunlight of fresh rhizome is carried out in order to obtain the dried Turmeric. The fingers are separated from the mother rhizomes. Mother rhizomes are usually kept as planting material. Separated fingers are boiled in water for three hours and then dried under sun light. The traditional method of curing involves the dipping boiling of fresh rhizomes in water taken just above the level of Turmeric till frothing occurs. Now the boiled material is filtered and dried under sunlight⁹.

Use of Turmeric in Ayurveda: Turmeric has been used ever since the time of the Vedas in medicine. The name Haridra itself is indicative of its action in Jaundice and other clinical conditions characterized by increased level of bilirubin giving rise to yellowish discoloration of the skin and mucous membrane along with the golden colour of the rhizome. The drug exhibits anti-allergic, anti-psoriatic, anti-leprotic, ulcer healing, hepato-protective, nephro-protective, anti-inflammatory, hematinic, hemo-styptic, weight reducing, anti-diuretic, urinary-discolourant, uterine tonic, breast milk purifier, semen purifier, anti-hiccup, anti-dyspnoeac, anti-poison, digestive, anti-anorexiant, carminative, anti haemorrhoidal, anti-helminthic, anti-pruritic properties on internal administration.

On this basis the drug is indicated in jaundice, fever, inflammation, edema, skeleto-muscular pain and sprain, wounds and ulcers, headache, migraine, vertigo, heaviness of head, rhinitis, hemicranias, epilepsy, diabetes and other conditions associated with polyurea, diarrhea (acute and chronic), jaundice, anemia, bleeding disorders, renal diseases, obesity, dyspnoea, cough, bronchitis, fever of all kinds, piles, flatulence, stomach pain, indigestion, allergy, poison, skin diseases including leprosy and psoriasis, eczema, ring worm, parasitic and fungal skin infections, scabies, gynaecological diseases, helminthes (worm infestation), joint diseases like rheumatoid arthritis, osteoarthritis, gouty arthritis etc. In ophthalmia neonatarum and conjunctivitis, decoction of Turmeric is applied over the eyes. The fumes of the burning turmeric relieve nasal congestion and cough and also for the treatment of scorpion sting and convulsive disorders.

The drug has to be administered along with jaggery and cow's urine in elephantiasis and ring worm, in diabetes along with Indian gooseberry juice and honey, in gout along with myrobalan decoction and honey, in anemia along with myrobalans powder and honey and clarified butter (Ghee) in unequal quantities. External application of the drug enhances the skin complexion, prevents and treats skin diseases, heals up the ulcers and wounds, bruises and cuts. It is also anti-allergic and anti-pruritic, analgesic and anti-inflammatory on external application.

On external application, it is also germicidal, disinfectant and anti-microbial in character. In Ayurveda the rhizomes are said to pacify Vata and Kapha Doshas ^{4, 5}. Milk boiled with Turmeric with or without sugar is given in cold, diarrhea, intermittent fevers, edema, jaundice, liver disorders, urinary diseases, worms, trauma and fracture. The fresh juice is used both as anthelmintic and also for bronchitis. The powder of rhizome mixed with the juice of Amla (Indian gooseberry) is used in diabetes and jaundice. The powder is given in fertilization and indigestion. The powder is also used as gum and dental troubles ⁵.

Dosage: Fresh juice obtained from fresh rhizome has to be taken in the dose of 10-20 ml per dose for two to three times a day. Powder of the dried rhizome has to be taken in the dose of 2-4grams once or twice daily depending upon severity of the disease and other factors considered for the determination of the dose. Decoction of the dried rhizomes has to be taken in the dose of 30-50 ml twice or thrice a day. Paste has to be administered, in the dose of 10-12 grams per dose once or twice daily. Various vehicles like honey, ghee or sugar can be added along with turmeric preparations in order to improve palatability, absorption and bioavailability ^{4, 5, 9}.

Specific formulations: Turmeric can be administered in various pharmaceutical forms of powder, paste, ointment, oil, lotion, inhalant, confections. Some of the important Ayurvedic formulation are Haridra Khand for allergic disorders, Vrana Shodhana Tailam for external application on wounds and ulcers, Nishamalaki Churnam for diabetes mellitus, Hardradi Ghritam for jaundice, Rajanyadi Lepam for inflammatory disorders, Rajanyadi Churnam for jaundice, elephatiasis, diarrhea, tropical sprue, fever and anemia, specifically of children ^{4, 5, 9}.

Chemical constituents: Turmeric powder contains about 67% carbohydrates, 12% water, 9% protein, 3% fat, 3-7% dietary minerals, 3-7% essential oils, 22% dietary fibers, 1-6% yellow coloring substances known as curcuminoids which are the main biologically active principles. This includes curcumin, bis-desmethoxy curcumin, desmethoxy curcumin. Out of these, curcumin is the most widely studied and pharmacologically active

principle. Approximately 34 essential oils are present in Turmeric among which turmerone, germacrone, atlantone, zinziberene are major constituents. Turmeric essential oil is also studied for a wide range of pharmacological actions. Other important constituents found in Turmeric are eugenol, eucalyptol, guiacol, borneol, L- α curcumene, L- β -curcumene, P-cymene, caryophyllene, curcumenol etc. Curcumin appears as orange-yellow needles ^{10, 11, 12, 13, 14}.

Bioavailability of curcumin: Despite Turmeric being very frequently used Ayurvedic medicine since time immemorial, poor oral bioavailability of curcumin (most important phytoconstituent of Turmeric) has become an important issue of discussion thus limiting the therapeutic efficacy of the drug. Poor bioavailability of curcumin has been attributed to its improper absorption, rapid metabolism and rapid elimination. Various initiatives including the use of liposomal curcumin, curcumin nanoparticles, curcumin phospholipid complex and use of bio-enhancers like piperine along with curcumin has been explored ¹⁵. Structural analogues of curcumin (like EF-24) ¹⁶, dimethoxycurcumin (DiMC) ¹⁷, FLLL-32 ¹⁸, Pyrozone and Isoxazole derivatives ¹⁹ have been discovered in order to overcome the issue of poor bio-availability.

These analogues have better absorption, biological efficacy; better metabolic stability and delayed elimination. The EF 24 is a synthetic analogue that exhibits stronger anticancer potential than curcumin ¹⁶. DiMC has better metabolic stability and is highly effective in arresting cancer cell cycles ¹⁷. FLL-32, another synthetic analogue blocks the STAT-3 signalling which is highly involved with tumor cell survival and proliferation ¹⁸.

Pyrazoline and Isoxazole derivatives have better selective and stronger COX-1 and COX-2 inhibition activity ¹⁹. Current researches for developing strategies for increasing bioavailability of curcumin in the human body is expected to change the therapeutic scenario of curcumin by expanding its therapeutic domain in diverse number of diseases. The nanoparticle form of curcumin administered by capsule form has been found to have at least nine times higher bioavailability than

combined administration of curcumin and piperine¹⁵.

Toxicity studies on curcumin: The single-dose oral administration of 5g curcumin/kg bw in rats did not result in any toxic effects and was 75% excreted in feces. Only 25% was absorbed into the circulation suggesting a poor bioavailability²¹.

In addition, oral toxicity studies using 2.5g/kg bw of whole Turmeric powder or 300 mg/kg bw of an alcohol extracts of Turmeric in guinea pigs, rats and monkeys did not result any toxicity. USA Food and Drug Administration (USFDA) approved Turmeric as Generally Recognized as Safe (GRAS)²². Curcumin has been reported to be safe for human use in large dosage (up to 12gms/day) in various phase -1 clinical trials¹⁴.

LD50: The reported acute LD50 of Curcuma- oil in rats exceeds 5 g/kg and the acute oral LD50 of curcumin is greater than 2g/kg bw²³. Dadhaniya *et al.* (2011) performed acute and subchronic safety assessments of Longvida (a highly bioavailable form of curcumin) in rats and mice. The oral LD50 in both rats and mice was found to be greater than 2000 mg/kg bw/day. In the subchronic toxicity study, the no observed adverse effect level (NOAEL) for Longvida was determined to be 720 mg/kg bw/day²⁴. Short-term safety studies of curcumin in animals have been well-reviewed²⁵.

Rats fed with 1.8 g/kg bw/day of curcumin for 90 days showed no adverse effects and while monkeys fed with 0.8 mg/kg bw/day for over 90 days also did not produce any adverse effects²⁶. In contrary to the above, a study found that, Turmeric can cause hepatotoxicity in mice and rats at high doses. A study in female Wister rats and Swiss mice fed with 0%, 0.01%, 0.1%, 0.2%, 1%, or 5% Turmeric and 0%, 0.05%, and 0.25% ethanolic Turmeric extract in the diet for 14 and 90 days. The administration of Turmeric for 90 days in high dose (5%) showed a significant weight reduction along with alterations in absolute and/or relative liver weight and hepatotoxicity ie focal necrosis or focal necrosis with regeneration both in mice and rats. In mice even lower dosage of Turmeric ie 0.2% or 1% for 14 days also showed hepatotoxicity. The study found that mice were more vulnerable to hepatotoxicity than rats²⁷.

Pharmacotherapeutic activities:

Anti-arthritis activity: In a 2023 systematic review and meta-analysis, safety and efficacy of curcumin was evaluated in consisting of 6 clinical reports on 539 rheumatoid arthritis patients. The study found that curcumin is beneficial for rheumatoid arthritis treatment by reducing the inflammatory markers like erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) and rheumatoid factor (RF), levels significantly along with improvement in clinical symptoms in terms of disease activity score (DAS), visual analogue scale (VAS), tender joint count (TJC) and swollen joint count (SJC) in the treatment group in comparison to the placebo control group²⁸.

This study was supported by two more meta-analysis in 2021 and 2022 which also concluded in similar way antagonistic to inflammation and arthritis. Another meta-analysis concluded that Curcumin when consumed in 120 mg to 1500 mg for a period of 4-36 weeks decreases both inflammation and pain in patients of variety of arthritic conditions like rheumatoid, osteo, juvenile, idiopathic, gouty arthritis and ankylosing spondylitis²⁹. Besides there are several *in-vivo* studies reported to justify the anti-arthritic activities of *Curcuma longa* Linn.

Hepatoprotective activity: Turmeric has been used in Kamalaa (jaundice) ever since the time of Vedas. There are innumerable *in-vitro*, *in-vivo* and clinical studies available to justify the hepatoprotective effects of turmeric. Ethanolic extract of rhizome has been found to provide protection in thioacetamide induced hepatic cirrhosis by reducing the level of pro-fibrotic cytokines like TGF- β 1 and pro inflammatory cytokine TNF- α . Along with suppressing the pro-inflammatory cytokines, turmeric protects the liver by exhibiting the anti-oxidant activities by enhancing the level of anti-oxidant enzymes³⁰.

It has also shown beneficial effects in alcohol induced and non-alcoholic fatty liver diseases. In alcoholic fatty liver diseases in animal models curcumin prevents the activation of NF-kB in Kupffer cells via endotoxins and suppresses the expression of various inflammatory cytokines, chemokines, cyclooxygenase-2(COX-2) and iNOS, as well as modulates the immune responses³¹.

Hepato-protective activities of turmeric and curcumin have been reported in various other models including CCl₄, isoretinoin, acetaminophen, bleomycin induced liver damage in animals. Curcumin and/or the whole turmeric have been able to reverse the hepatic damage induced by the above hepato-toxins by reversing the altered parameters like aspartate amino transferase (AST), alanine aminotransferase (ALT), malondialdehyde (MDA) along with increasing the level of antioxidant enzymes like superoxide dismutase (SOD) and glutathione (GSH) along with modulating the pro-inflammatory cytokines like IL-1 β , IL-6, TNF- α , IFN- γ , cyclooxygenase-1&2(COX-1&2)³².

In a systematic review and meta-analysis which included randomized controlled clinical trials, in patients with non-alcoholic fatty liver diseases (NAFLD), curcumin significantly reduced the AST, ALT, MDA, total cholesterol(TC), low density lipoprotein (LDL), fasting blood sugar(FBS), homeostatic model assessment of insulin resistance(HOMA-IR), serum insulin and waist circumference³³.

Anti-diabetic activity: Mutations in the KCNJ-11 gene (kir6.2) channel are reported to be associated with congenital hyperinsulinism, having a major impact in causing neonatal diabetes of transient type and permanent type and also the developmental delay, epilepsy and diabetes (DEND) syndrome. Heterozygous mutations in the human Kir 6.2 gene (KCNJ11), the pore-forming subunit of the ATP-sensitive K (ATP) channel, cause permanent neonatal diabetes mellitus (PNDM)^{34, 35}. Curcumin was interacted with both the normal and mutated Kir 6.2 gene and it was found that curcumin, piperine, pterostilbene and genestein have strong affinity for both normal and as well as mutated Kir-6.2 genes in a molecular docking study. Curcumin and other phyto-molecules can play a significant role in the treatment of neonatal diabetes of transient, permanent and DEND types. Kir 6.2 channels have also been recognized as a potential target for drug development for the treatment of Type-1 diabetes mellitus (Type-1 DM)³⁶. The role of auto-antibodies in the genesis of Type-1 DM is well established. Curcumin suppresses the pancreatic infiltration of leucocytes and keeps the insulin producing β cell mass intact in the murine models

of Type-1-DM. This activity gives rise to the suppression of autoimmune mechanism responsible for Type-1-DM. Curcumin impairs the pro-inflammatory T-9Helper-1 (TH-1) cell proliferation, differentiation which gives rise to reduced secretion of diabetogenic interferon- γ (IFN- γ) production by modulation of T-box protein expressed in T cells (T-bet), a master regulator of inflammation. Also, curcumin reduces nuclear factor (NF)- κ B activation on T cell receptors (TCR) in non-obese diabetic (NOD) mice. In addition, curcumin impairs the T cell stimulatory function of dendritic cells with reduced secretion of proinflammatory cytokines and nitric oxide (NO) and low surface expression of co-stimulatory molecules, leading to an overall diminished antigen-presenting cell activity³⁷. On the other hand curcumin and/or whole or fractionated extracts of Turmeric have been found to inhibit the over-expression of both NF κ B and TNF- α in pancreatic β cells thus eligible to play a significant role in the prevention and control of both type -1 and 2 diabetes which over express these two pro-inflammatory molecules^{38, 39}.

On mesenchymal stem cells and regenerative medicine: Mesenchymal stem cells (MSCs) have a tremendous efficacy in immune related conditions specifically in autoimmune diseases, graft versus host diseases, Crohn's disease, multiple sclerosis, systemic lupus erythematosus, systemic sclerosis etc. They are known to promote the regeneration of pancreatic islet β cells. Mesenchymal stem cell modulation ability of curcumin is a breakthrough result which has consequences for its use in both type -1 and type- 2 diabetes mellitus^{40, 41}. Genes such as OCT4 and SOX2 are closely related to the self-renewal and proliferation of MSCs Curcumin can modulate the proliferation, differentiation and migration of (MSCs) by regulating multiple signaling pathways like Wnt/beta-catenin, MAPK, NF- κ B, and AMPK⁴². *In-vitro* experiments suggest, low concentration of curcumin usually promotes proliferation and inhibit apoptosis, while high concentrations may inhibit cell growth or induce cytotoxicity⁴³.

Cardioprotective activity: Curcumin exhibits cardio-protective activity by modifying the cardio-risk factors including hypertension, stroke, atherosclerosis and other ischemic cardiac

conditions. It works by the anti inflammatory, anti-oxidant mechanisms and by interacting with nitric oxide (NO) bioavailability which is a prime factor in the myocardial contractility. Curcumin promotes endothelial nitric oxide synthase (eNOS) activity and prevents oxidation induced destruction of the available NO in the cardiac tissues and vascular endothelium. This directly promotes vasodilation, regulates blood pressure and improves overall endothelial function. Curcumin modifies cell adhesion by modifying various inflammatory markers like NF- κ B/PI3K/AKT, MAPK/NF- κ B/IL-1 β , Heme oxygenase-1(HO-1), Nitric oxide synthetase (NOS), vascular endothelial growth factor (VEGF), Intracellular adhesion molecules-1(ICAM-1) and reactive oxygen species (ROS) in the cardiac muscles⁴⁴.

Nephroprotective activity: The reno-protective effect of curcumin has been evaluated in several experimental models including diabetic nephropathy, chronic renal failure, ischemia and reperfusion and nephrotoxicity induced by compounds such as gentamicin, adriamycin, chloroquine, iron nitrilotriacetate, sodium fluoride, hexavalent chromium, cisplatin and copper sulphate. The major mechanism behind the renoprotective activity of curcumin is its anti-oxidant and anti inflammatory activity along with the reversal of glomerular haemodynamical changes observed after the administration of reno-toxic agents even in chronic renal failure. Curcumin over activates the Nuclear factor erythroid-2 related factor (NRF-2) which is a master cellular regulator and protects the body from inflammation and oxidative damage. It activates hundreds of anti-oxidant and cytoprotective genes to maintain cellular homeostasis. In kidney diseases NRF-2 defends against the oxidative damage, inflammation and renal fibrosis. Curcumin activates NRF-2, which protects against acute kidney injury and significantly protects against renal ischemia reperfusion injury in animal models. In contrast, chronic NRF-2 activation may exacerbate proteinuria, fluid retention, blood pressure and some existing forms of cancers^{45, 46, 47}.

Anti-allergic activity: Turmeric has been extensively used in allergic diseases in ancient Ayurvedic literature. In a randomized double blind

human study, oral administration of curcumin for two months significantly declines the level of TNF- α and IL-8 in patients of allergic rhinitis. Clinically curcumin prominently reduces the nasal symptoms like rhinorrhoea, sneezing, itching and obstruction and remarkably improved the nasal congestion by reducing nasal airflow resistance⁴⁸. Another clinical trial in children and adolescents with persistent asthma indicated that using powdered rhizome of *Curcuma longa* L for six months resulted better disease control⁴⁹.

Curcumin has been known to reduce the histamine release from mast cells which is primary mechanism behind allergic reactions. In murine model of chronic asthma, curcumin suppress the recruitment inflammatory cells along with inhibiting the level of IgE and inhibition of proinflammatory cytokines like IL-4 and IL-5⁵⁰. In murine food allergy models, curcumin inhibits the level of IL-4, IL-5, IL-13, IL-9 and IL-10⁵¹. In mouse models of allergic rhinitis curcumin directly reduces the production of IL-4 and IgE and enhances the IFN- γ levels which in turn suppresses IgE production and reduces the activity of the eosinophils⁵².

Anticancer effect: Turmeric derivative curcumin and turmeric whole extract have been reported to exhibit anti cancer effect in several cancer cell lines *in-vitro* and also against several chemical induced carcinogenesis *in-vivo*. Simultaneous cytotoxic, anti-proliferative, anti-invasive, apoptotic and anti-metastatic activities have been reported from curcumin. It has been found to inhibit the growth of cancerous cells in breast, lung, prostate, leukemia, pancreatic, gastric cancer cell lines and many others. Its anticancer effect has been mediated through the inhibition of various inflammatory, proliferative, metastatic, invasive, angiogenic, tumor forming pathways along with upregulation of various cytotoxic, apoptotic, DNA repairing pathways thus giving rise to inhibition of uncontrolled cell division, tumor formation and progression, metastasis, invasion and angiogenesis. The major signaling pathways curcumin inhibits are NF- κ B (lung, breast, prostate, head and neck squamous cell carcinoma), VEGF(lung cancer), Akt(breast, gastric cancer), mTOR(breast cancer), MAPK/ERK (prostate, gastric cancer), EGFR (prostate cancer), PI3(gastric cancer), ERK, PDGF

(pancreatic cancer), STAT-3(head and neck squamous cell carcinoma) etc. Inhibition of these cell signaling pathways have resulted in down regulation of cancer related genes like BCL-2, BCL-xL, IL-6, COX-2, miR-210, p53, Ras, Wnt- β , PI3K and Akt in various cell lines of the respective cancers^{53, 54}.

Immunomodulatory activity: It has been evaluated for its immunomodulatory activity within the domains of antioimmune, inflammatory, allergic and proliferative diseases. The immunomodulatory activity of curcumin has been ensured by the enhancement of total white blood cell (WBC) count, circulating antibody titer against sheep red blood cells (SRBC) and total plaque forming cells (PFCs) in the spleen against SRBC and bone marrow cellularity in Balb/c mice along with a significant increase in the macrophage phagocytic activity in comparison to control⁵⁵. In a separate experiment, nanoparticles of curcumin has stimulated the primary humoral immune response in terms of antibody titer while the plain curcumin has suppressed it, in albino mice sensitized with SRBC when administered in the dose of 5mg/kg bw/day for 10 days⁵⁶.

An aqueous extract of whole turmeric in the name of NR-INF-02 has significantly increased the splenocyte number in the presence or absence of Concanavalin A or lipopolysaccharide (LPS), nitric oxide (NO), IL-2, IL-6, IL-10, IL-12, IFN- γ , TNF- α and MCP-1 production in un stimulated mouse macrophages and splenocytes. Further mother liquor portion of NR-INF-02 has significantly inhibited the PGE2 and IL-12, an inflammatory cytokine in LPS stimulated splenocytes justifying its anti-inflammatory and immune-modulatory action *in-vitro*⁵⁷. The antiallergic activity of curcumin is mediated through the suppression of mast cell degranulation and release of histamine and also suppresses the release of pro-inflammatory cytokines like IL-1- β , TNF- α , IL-6 from LPS stimulated dendritic cells. Curcumin also suppresses CD-80, CD-86 and MHC class-II antigens by the dendritic cells⁵⁸.

Anti-inflammatory response: Curcumin is a potent anti-inflammatory agent. It works through various pathways to suppress inflammation. These include the suppression of the most important

molecular inflammatory pathway NF-kB along with suppressing the COX-2 and LOX enzymes responsible for secreting inflammatory mediators like prostaglandins and leukotriene. Suppression of cellular markers like TNF- α , IFN- γ , C-reactive protein (CRP), IL-1, IL-1 β , IL-6, IL-8, IL-17, IL-etc is another mechanism of its anti-inflammatory activity. In a double blind randomized placebo controlled trial, 80 mg curcumin nanomicelle given daily has improved the C-reactive protein significantly in the blood plasma. Many other clinical trials are available which have substantiated the anti inflammatory activity of curcumin or whole turmeric by establishing its anti-arthritic, anti cancer, anti-Alzheimer's, anti-atherosclerotic activity. A common pathology which determines the clinical sequel of these diseases is inflammation⁵⁹.

Anti-asthmatic activity: Curcumin regulates cytokine levels such as IL-4, IL-5, TNF- α , IL-13 which are responsible for the airway inflammation and allergic effect in bronchial asthma. The drug also inhibits mast cell degranulation and prevents lipid peroxidation in lungs⁶⁰.

Pharmacotherapeutic activities of turmeric oil: Similar kinds of activities have been recorded for Turmeric essential oil (TO). It has shown anti inflammatory activities by suppressing the NF-kB signaling pathway and pro-inflammatory cytokines like TNF- α . It has scavenging activities on the oxidative free radicals by inhibiting superoxide generation triggered by phorbol-12-myristate-13-acetate in mice after IP 12 administration. Oral administration of the Turmeric essential oil for 30 days resulted in the significant increase in the glutathione level along with increase in anti-oxidant enzymes like superoxide dismutase (SOD), glutathion reductase in plasma and liver (along with glutathione S transferase)⁶¹.

The anti-inflammatory activities of TO is comparable to that of diclofenac, a standard anti-inflammatory drug in formalin induced mice paw thickness⁶¹. Its anti inflammatory activity is also comparable to that of aspirin, in carrageenan induced rat paw edema⁶². TO activates caspase-3 and 9 ultimately resulting in increased apoptosis in murine model of benign prostatic hyperplasia and in human skin cancer cells^{63, 64}.

Its suppressing effect on the NF-kB signaling pathway partly explains its anti-cancer effect because activation of NF-kB pathway plays a significant role in inflammation, angiogenesis, oncogenesis and cancer therapy resistance^{64, 65}. Besides TO has shown anticancer effects in cervical cancer cell lines *in-vitro* and in primary hepatic carcinoma *in-vivo*. Various compounds isolated from TO have shown diverse biological activities. Eucalyptol has shown *in-vivo* nephroprotective activity, AR-turmerone has neuroprotective, cardioprotective, analgesic, anticancer, anti-diabetic, anti inflammatory, nephroprotective, antibacterial, antifungal, antiparasitic, insecticidal activities either *in-vitro* or *in-vivo*⁶⁶. TO exhibits anti-diabetic effect by reducing the blood sugar, triglyceride, total cholesterol, LDL, malondialdehyde, IFN- γ , IL-6, CRP levels along with increasing insulin level in the circulation in murine models⁶⁷. TO from fresh and dried rhizomes showed a higher glucosidase inhibition than acarbose. The oil obtained from the dried samples was reported to be 3.5 times better than that obtained from fresh samples⁶⁸.

CONCLUSION: A panacea is a drug which has “all curing ability”. Turmeric in the system of Ayurvedic medicine has been indicated in a diverse number of diseases of respiratory system, digestive system, skeleto-muscular system, endocrine system, immune system, cardiovascular system, urinary system, nervous system and skin. In the digestive system, it stimulates the digestive fire, heals up the stomach ulcer and cures jaundice. In respiratory system it possesses anti-asthmatic and anti-allergic activity. On endocrine system it has potential anti-diabetic activity which is mediated through the suppression of the inflammation and autoimmunity pathways resulting in reduced β cell damage and improved quality of life along with blood sugar lowering activities in both Type-1 and Type-2 DM. Higher bio-available congeners of curcumin are expected make a breakthrough in the forthcoming anti-diabetic therapy along with therapies in diseases of other systems of the body. Its diverse role on immunological system includes anti-allergic, autoimmune suppression, humoral immunity stimulation and suppression of cytokine axis of inflammation. These actions qualify Turmeric to be used in wide number of diseases like arthritis, allergy, systemic lupus erythematosus

(SLE), psoriasis, eczema, common cold, rhinitis, bronchial asthma, arteriosclerosis etc. Its MSC proliferative action can partly explain its use in graft versus host diseases, Crohn's disease, multiple sclerosis, SLE, Type-1 and Type-2 DM and also various forms of cancers. Its anti-fibrotic action makes it an eligible candidate to be used in liver cirrhosis and also in renal fibrosis. Its anti-inflammatory role makes it a powerful candidate for the treatment of various inflammatory diseases of different systems such as arthritis of various types, arteriosclerosis, hepatitis, nephritis, Alzheimer's disease, Parkinson's disease, cancer, bronchial asthma, bronchitis etc. Present review reveals Turmeric is categorically effective in resolving varieties of strategic disease causing mechanisms like inflammation, auto-immunity, allergy and hypersensitivity, oxidative stress, cellular proliferation, tumor formation and microbial infections. Therapeutic uses of Turmeric and its derivatives can be extended to all kinds of diseases falling under these pathological categories.

Among these, diseases due to inflammation, oxidative stress, allergy and microbial infections are frequently encountered in clinical practice. Turmeric and its derivative including curcumin and Turmeric oil have potential role in the treatment of diseases arising out of these four pathological mechanisms on the basis of available evidences from *in-vitro*, *in-vivo* and clinical studies. Incidences of diseases due to cellular proliferation and tumor formation are going to increase very fast in India and abroad. Turmeric and its derivatives perhaps are going to be a boon for the prevention and treatment of proliferative and tumor associated disorders on the basis of available evidences either as monotherapy or along with traditional anti-proliferative therapies. Current route of administration of Turmeric has been confined to oral route only which has the limitations such as poor bioavailability, short duration of action and short elimination half life. Parenteral dosage form of Turmeric or curcumin is still a distant dream. This study proposes Parenteral preparations of Turmeric and derivatives, specifically the injectible form which will resolve the issue of lower bioavailability and short half life period. These preparations may be strategic for immediate onset of action and augmented potency of the drug. However these injectible preparations have to

undergo rigorous preclinical and clinical trials before being marketed for respective clinical conditions in which Turmeric has been indicated, but are expected to change the interface of pharmacological interventions in inflammation, allergy, autoimmunity, microbial infections, and proliferative and oxidative stress disorders. The study also proposes randomized double blind controlled clinical trials for Turmeric and its various derivatives in order to justify the therapeutic claims made in Ayurveda. Available literature evidences and wide range of pharmacotherapeutic activities justify Turmeric to be equivalent to a “a panacea, a universal remedy for all kinds of diseases”. This statement holds good and is verifiable.

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