ABSTRACT

Turmeric (*Curcuma longa*) is well known Ayurvedic herb has been practicing for the treatment of various ailments, i.e., fever, inflammation, sore throat, fresh wound healing, and it is observed that most of the time the turmeric is used in Ayurveda along with milk or cow butter. The myriad benefits of turmeric have been widely studied and proven. The problem with turmeric supplementation is that the active components, curcuminoids, are very poorly absorbed. A pure turmeric extract will not reach the blood supply in any meaningful or therapeutic level. Its effects, while still quite powerful, will be limited to the intestines. It is so poorly absorbed in fact that in one study even at a dose of 2g/kg, blood levels of curcuminoids were barely detectable, if at all.\[1\] For a 150 pound person that means eating almost a third of a pound of turmeric will still not result in significant systemic distribution. In response, the supplement industry has spent millions of dollars to bioengineer products with improved assimilation. Thousands of years ago in India, Ayurveda developed techniques that greatly enhanced the absorption of haldi as it is called. There are two widely accepted methods to increase turmeric absorption; take it with some kind of fat, or with black pepper, or more specifically piperine. Most available preparations for turmeric that boast increased assimilation are based on these methods. Curcuminoids are lipophilic substances. This means that they will not dissolve in water which makes them poorly absorbed by our intestines. However, they do dissolve in fats which are themselves readily absorbed by the intestinal lining for absorption and utilization. Turmeric is just along for the ride. Hence the use of phospholipid phytosomes and other creative approaches using fatty substances for increasing absorption in many modern turmeric preparations. *Piper nigrum*, or black pepper, contains the alkaloid piperine, which gives pepper its distinct spicy flavor. This compound inhibits glucuronidation. Glucuronic acid is added to molecules by the
body to make them more water soluble which allows the kidneys to remove them from the body. This process is very prevalent in both the intestinal lining and the liver in order to protect the body from possibly toxic molecules that are ingested. Piperine inhibits glucuronidation in both the intestines and the liver. This allows high levels of curcuminoids to enter the blood flow in their active form. In fact, adding piperine to a turmeric supplement can increase absorption by 2000%. That is a mind boggling number! Where did the scientists have come up with the crazy idea. It happen due to observing the traditional ways turmeric was consumed in Indian culture! Keeping these views in mind the recent developments in Drug Delivery, Bioavailability, Absorption and Metabolism of Curcumin was studied literary and presented for further needful.

**KEYWORDS**: Curcumin, Curcuma longa, Piper nigrum, Haridra, Glucuronidation,

**INTRODUCTION**

Medicine is as old as human life itself because the survival of any species requires that all living things must develop the means to combat disease and optimize health. In the early times of human evolution, people lived in the heart of nature, using all their senses to test and observe the effects of different plants on their health and wellbeing. They evolved their knowledge through trial and error, accidentally as well as inspirationally. Through time these insights became structured into organized systems where a deep understanding of nature led to our ancestors evolving a language and understanding of health and disease. As this detailed knowledge of how to use certain plants for specific ailments became passed from generation to generation the origins of human medicine were born and Ayurveda is one of the earliest and longest surviving organized systems.

Ayurveda, the system of medicine originating in India, has survived as a distinct entity from remote antiquity until the present day. Ayurveda is literally translated as ‘science of life’, it can also be interpreted as ‘the way of living with awareness and promoting longevity’ described in its oldest known texts Charaka Saṃhitā and Suśrutha Samhitā (200 BCE and 300 CE). It is called Ayurveda because it tells us which substances, qualities and actions are life enhancing, and which are not.[1]

It is based on three fundamental principles: vāta, pitta and kapha dosha which comprise the five elements: earth, water, fire, air and ether; these are the components of everything we are and are surrounded by. Vāta is responsible for controlling movements with in the body. For
example, because of the principle of ‘like increasing like’, if there is dry-cold-windy weather it will increase the dry-cold-‘windy’ qualities in an individual with high vāta. This additional wind can lead to dryness of the skin, constipation and insomnia as the main qualities of vāta are dry, cold and light. Fortunately, and largely thanks to the insights of our ancestors, there are many methods to counteract these imbalances: a simple cup of licorice and/or cinnamon tea, a warm bath or a massage with warm oil (preferably almond oil or any oil with vāta reducing herbs like Mahararanyam oil). It is as simple as that…

The fundamental principles on which the Ayurvedic system is based are time-tested but it has also evolved as and when new knowledge has been learnt. Both basic and clinical research dates back to at least Avicenna, a Muslim scientist of the tenth and eleventh centuries.[2] However, in the Eastern Han period, a medical scientist of Traditional Chinese Medicine named Zhang Zhongjing (150 CE - 219 CE), wrote a sixteen volume work entitled Discussion of Cold Induced Disorders (Shanghan Lun) including the areas of epidemic, external heat disorders, jaundice, gynecology; this document set down a complete set of treatment principals based on clinical experience. Zhang Zhongjing’s theory and prescriptions are still of great practical value today.[3]

A great change however, happened in the late 1800s when chemistry was advancing and the focus of those involved in development of medicines changed from whole herb use to single isolated compounds contained within the plant. The responsibility for herb quality passed from herbalists to medical doctors and the materia medica, was generally replaced by pharmacology and pharmacognosy - specializing in the development of drugs from natural products which was then codified into national pharmacopoeias. Subsequently, pharmacopoeias as a quality standard for drugs within national health care approval systems were based on the needs for modern drugs, not traditional herbal medicines.

At the same time, the focus changed to research, specialization and high-cost drug approval processes; a medical system more driven by research findings and profits than practitioner or patient need.[4]

In contrast to that, the medical theories of Ayurvedic and Chinese herbal medicine remain intact, continue to evolve, and continue to be practiced according to their same historical foundational principles.[5] There is now the opportunity for the scientific community to review the emphasis on the quality of the whole plant material itself rather than viewing
herbal drugs as cocktails of chemicals to be pulled apart, isolated, and manipulated – a process accompanied with high risks leading to serious and fatal adverse drug reactions (ADRs). A meta-analysis on the incidence of (ADR) in hospital patients in the US, demonstrated overall 2,216,000 hospitalized patients had serious ADRs and 106,000 had fatal ADRs in one year, making these reactions between the "Evidence-based Medicine" is being used to validate the use of modern drugs as well as time-honored herbal remedies. However, we must be aware to not lose sight of the whole plant while analysing quality marker compounds and other the research findings. Moreover, we should focus on finding new ways to analyse the complex nature of herbal medicine, so that an alternative for health care approval systems can be provided which is meeting the needs of traditional herbal medicines.

In the 1990, the term "Evidence-based Medicine" (EBM) first appeared and was created to integrate individual clinical expertise with the best available external clinical evidence from systematic research. It was the consequence of dissatisfaction how research results were incorporated in medical decisions. The first modern step in the development of EBM was the advent in the 1950s of the randomized trial (RT) as a methodology for resolving therapeutic dilemmas. Chief among these dilemmas are the recognition of problems associated with the use of more subjective forms of evidence regarding new pharmaceuticals and unknown side-effects (eg. expert opinion unsupported by systematic research, uncontrolled observations). Documented reports of such failures are numerous: some agents with inotropic properties, despite physiologic promise, actually increase mortality. Similarly, some antiarrhythmic agents have been shown to both eliminate non-cardiac arrhythmias and increase mortality. And maybe one of the biggest catastrophes: the unknown teratogenic effects of thalidomide in the late 1950s: a failure to demonstrate teratogenic effects experimentally in animal experiments did not prove the drug's harmlessness to the human embryo- 10,000 cases of infants with phocomelia due to thalidomide were reported; only 50% survived.

Grünenthal, a pharmaceutical company began marketing its new “wonder drug” as a sleeping pill and morning sickness preventative especially for pregnant women in 1957 as safe, though it had never tested the drug on pregnant animals not to mention in humans. EBM should ensure a more rigid process to guarantee safety and efficacy of medicinal drugs. Materia medica is the Latin medical term for the body of collected knowledge about the therapeutic properties of any substance used for healing derived by the Ancient Greek physician Dioscorides in the 1st century AD. The term materia medica was used from the period of
the Roman Empire until the 20th century, but has now been generally replaced in medical education contexts by the term pharmacology.

**Turmeric, the ancient golden spice finally gets its well-deserved recognition**
Turmeric’s history goes back over 2000 years, to the heyday of Ayurveda. Sushruta Samhita, dating to about 200 BCE, recommends a turmeric ointment to relieve the effects of consuming poisoned food and for wound healing.\(^{[14]}\) Turmeric’s efficacy and safety was monitored through simply observing. Turmeric is prevalent in both formulations and oils, these have been adapted and developed on experience. As we have just seen, analytical and clinical research dates back at least to Avicenna (around 1000 CE).\(^{[15]}\) and as experimentation, science and technology became established, laboratory analysis gained momentum. Chemical analysis has so far uncovered hundreds of thousands of natural plant compounds. There are approximately 235 compounds in turmeric.\(^{[16]}\) By means of modern science based medical research, the benefits of turmeric are being confirmed and the mechanisms of its action more deeply understood. Turmeric derived from the rhizome of the plant Curcuma longa and has been used by the people of the Indian subcontinent for centuries with no known side effects, not only as a component of food but also to treat a wide variety of ailments.\(^{[17]}\) Today, turmeric is reaching new levels of awareness and respect. As is so often the case, extensive preclinical and clinical research on turmeric over the past few decades has confirmed most of its traditional uses. Modern medical findings include antioxidant, anti-inflammatory, anticancer, antigrowth, anti-arthritis, anti-atherosclerotic, antidepressant, anti-aging, antidiabetic, antimicrobial, wound healing, hepato-protective and memory-enhancing activities (which can be linked to its Ayurvedic actions described in the old texts of Charaka Samhitā (Table 1, Figure 1)).\(^{[18]}\) (A,B) From the traditional Ayurvedic point of view, turmeric is popular for its ability to balance all three constitutional dosha to a healthy equilibrium making it a mainstay of everyday health.
Table 1: Linking traditionally experienced properties of turmeric with modern science based medicine.

<table>
<thead>
<tr>
<th>Sanskrit</th>
<th>Meaning</th>
<th>Potential uses of turmeric based on modern science**</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lekhanīya</td>
<td>‘Scraping’ property</td>
<td>Gall stone, Hypolipidemia</td>
</tr>
<tr>
<td>Dīpana</td>
<td>Enkindles the digestive fire</td>
<td>Hypothyroidism</td>
</tr>
<tr>
<td>Prameha</td>
<td>Useful in diabetes</td>
<td>Diabetes</td>
</tr>
<tr>
<td>Pāṇḍughna</td>
<td>Used in Anaemia</td>
<td>Fanconi anemia</td>
</tr>
<tr>
<td>Raktaśodhana</td>
<td>Blood purifier</td>
<td>All inflammatory diseases eg. Arthritis, Inflammatory bowel disease, Pancreatitis, Allergy, Cancer, Gastric Ulcer</td>
</tr>
<tr>
<td>Ārtavajanana</td>
<td>Promotes Menses</td>
<td></td>
</tr>
<tr>
<td>Jvaraghna</td>
<td>Alleviates fever</td>
<td>Fever</td>
</tr>
<tr>
<td>Viṣaghna</td>
<td>Destroys poisons</td>
<td>Malaria, Leishmaniasis, Antihelminthic</td>
</tr>
<tr>
<td>Kuṣṭhagna</td>
<td>Removes skin diseases</td>
<td>Psoriasis</td>
</tr>
<tr>
<td>Kaṇḍūghna</td>
<td>Stops itching</td>
<td>Psoriasis</td>
</tr>
<tr>
<td>Vedanāstahāpana</td>
<td>Analgesic</td>
<td>All painful diseases</td>
</tr>
<tr>
<td>Sandhānīya</td>
<td>Heals broken bones</td>
<td>Osteoporosis</td>
</tr>
<tr>
<td>Śirovirecana</td>
<td>Clearing stagnation from the head</td>
<td>Multiple sclerosis, Epilepsy, Alzheimer’s, Parkinson’s</td>
</tr>
<tr>
<td>Stanyaśodhaka</td>
<td>Purifies breast and breast milk</td>
<td></td>
</tr>
</tbody>
</table>

Inflammation – the trigger of most diseases

The breakthrough in modern turmeric research likely occurred when its anti-inflammatory activity was demonstrated in 1971. The effect of turmeric was comparable to that of hydrocortisone, a steroidal drug prescribed for the treatment of many inflammatory and allergic conditions.[19]

As we would expect for such a ubiquitous health problem, the recognition of inflammation dates back to ancient times. As documented by Celsus, a Roman doctor in the 1st century CE, the ancients understood that the tissue response to injury gave rise to rubor (redness, due to hyperemia), tumor (swelling, caused by increased permeability of the microvasculature and leakage of protein into the interstitial space), calor (heat, associated with the increased blood
flow and the metabolic activity of the cellular mediators of inflammation) and dolor (pain, in part due to changes in the perivascular and associated nerve endings).[20] In Ayurveda, inflammation is categorized according to its own specific anatomy, physiology and pathology involving the pitta dosha, and various tissues especially including the plasma rasa dhatu and blood rakta dhatu tissues.

Inflammation provides a unifying pathophysiological mechanism underlying many chronic diseases, including diabetes, cardiovascular disease, certain cancers and bowel diseases, dementia, arthritis and osteoporosis. Common pathophysiologic scenarios apply to many of these diseases.[21] Mastery of the inflammatory response should aid the prevention and treatment of these chronic diseases.

Taking a closer look: Whole spectrum of Turmeric rather than Curcumin

Turmeric is chemically diverse: so far approximately 235 compounds have been identified including polyphenolic, terpenes and volatile oils. Curcumin is just one compound that gives the yellow colour to turmeric.[22] It was first isolated two centuries ago and has been extensively studied in the last century. Early on in the clinical research into turmeric all of the activities ascribed to it were associated with curcumin. However, more recent studies have identified that curcumin-free turmeric components possess also numerous biological activities including anti-inflammatory, anticancer and antidiabetic activities.[23] This comes as no surprise to traditional medicine; turmeric, known as jiang huang in China, has long been used effectively as a water decoction in Traditional Chinese Medicine (TCM). As the non-polar curcumin is poorly absorbed in water the other compounds in turmeric would have to be responsible for its potent pain relieving properties for which it was used.

The analysis of a UK leading turmeric product (WTE) made from a whole turmeric extract including concentrated curcumin, essential oils and whole turmeric root in comparison with a UK leading concentrated 95% curcumin product (CE) demonstrates the health benefits of the whole spectrum of turmeric and also that it is not just about the curcumin. Brunswick Laboratories (U.S.) analysed the impact of WTE vs. CE on specific proteins in a human cell line study. Nrf2, NF-kB and COX-2 (please find more details in the box below) are naturally present in humans and have a key role in specific pathways, impacting inflammation, aging, pain and disease causation and prevention. The extent of the impact is dependent upon their activation levels, it’s like a dimming rheostat which could either be turned on to its full potential, switched off or anything in between.
For example, in the case of Nrf2, a multi-organ protector, ideally it would be fully activated in the body as it reduces inflammation, supporting the detoxification process and activating antioxidant responses. Whereas NF-kB, a transcription factor which triggers inflammation, and COX-2, an enzyme responsible for swelling and inflammatory pains, would preferably be fully dimmed.

The study found that the activity of multi-organ protector Nrf2 is enhanced by 76% when treated with WTE. To achieve this level of activation with CE*, four times as much product must be used. Nrf2 truly deserves its name multi organ protector because it plays a vital role in cells. It maintains cellular homeostasis, detoxifies enzymes and reduces inflammatory responses, which is crucial for disease prevention, supporting the healing process and to slow aging. Especially important is Nrf2’s ability to limit cell exposure to chemical or oxidative stress, through regulation of antioxidant proteins.

The treatment with WTE shows an inhibition of NF-kB by 66% and this effect was 2.6 times more than that of CE**. Furthermore, COX-2 is inhibited by 60% when treated with WTE, with up to 10 times greater inhibition vs. CE and even 5.5 times better than paracetamol which is popular for its inhibition of COX-2***. In both cases, the dimming rheostat was turned down from 100% to 34% and 40% respectively, indicating that WTE reduces inflammation and pain significantly and more effectively than CE and paracetamol do.

A recently published study reports that Acetaminophen (Paracetamol) reduces people’s empathy for the pain of others. Paracetamol is an ingredient in over 600 different medications, including being the main constituent of Tylenol which is taken by a quarter of US adults each week. Dr. Dominik Mischkowski, the study’s first author said that the ubiquitous painkiller does not just kill pain, it also kills our fellow-feeling in two double-blind placebo-controlled experiments with 80 participants.[24]

However, these results are not surprising considering research which indicates curcumin-free turmeric is as effective as, or even more effective than isolated curcumin products showing that a WTE extract that combines the full spectrum of Turmeric’s 230 compounds is the most effective of them all.[25]

There are several reasons why we should consider using the whole spectrum of turmeric rather than only the pure curcumin: turmeric contains more than 200 bioactive compounds.
which are beneficial to your health. None of this goodness is present in any simple curcumin products. By taking isolated curcumin, you would forego the benefits of turmerones (part of the essential oil) which not only significantly enhances the absorption and transport of curcumin but are proven to exhibit anti-inflammatory and anticancer activities and support regeneration in neurologic disease.\textsuperscript{26}

**Nrf2 (Nuclear factor (Erythroid-derived 2)-like 2)**

Nrf2, Nuclear factor (erythroid-derived 2)-like 2, is involved in cellular responses to oxidative damage triggered by injury and inflammation and plays a key role to manage various pathways and protects the various organs in the body as the name multi-organ protector already demonstrates.

Nrf2 is transcendental in the regulation of various cellular processes, such as antioxidant defences, redox equilibrium, the inflammatory process, the apoptotic processes, intermediate metabolism, detoxification, and cellular proliferation\textsuperscript{27} and furthermore up regulating its activity is a strategy for cancer chemo-preventive phytochemicals.\textsuperscript{28} Numerous studies have shown this Nrf2-conferred, multi-organ protection phenomenon protects many cell types and organ systems from a broad spectrum of toxic insults and disease pathogenesis.\textsuperscript{29}

It was found that Nrf2 has an antagonistic effect on the NF-κB pathway (Cuadrado A. et al. 2014).\textsuperscript{30} When Nrf2 is activated, NF-κB pathways is also mediated and concurrently down regulated showing how such multiple interactions allow bioactive compounds, including turmeric, to exert their beneficial preventive and therapeutic effects.

NF-κB (nuclear factor 'kappa-light-chain-enhancer' of activated B-cells), a protein complex that plays a key role in regulating the immune response to infection. Inhibition of NF-κB limits the production of pro-inflammatory gene expression and reduces the level of inflammation, therefore NF-κB has been studied as a biomarker for inflammation, and inhibition of NF-κB has been used as an indicator for anti-inflammatory potential.

COX-2(Cyclooxygenases-2 inhibitors) are among the important targets for treatment of inflammation related diseases. It is reported that selective COX-2 can target inflammation and pain with reduced risk of chronic ulceration and acute injury.
Overwhelmed by choice – choosing the right one

With so much choice it is difficult to choose the right turmeric on the market. Here are some tips in making the correct decision. Buy whole turmeric root extracts with whole turmeric root instead of an isolated curcumin product, to make sure that you do not miss out any additional benefits from the multiple compounds in whole turmeric. I recommend taking an organic product, as you do not want to spoil the advantages of turmeric with harmful chemicals like pesticides that are so often used in growing conventional turmeric. Avoid dangerous chemical residues – such as hexane, methanol and acetone - from industrial curcumin extraction methods, gelatine – important to avoid for vegetarians and vegans - and harmful emulsifiers like polysorbate 80 (Tween 80) that have been tested in animals and are used to supposedly enhance curcumin’s bioavailability 185 times. A recently published article in ‘Nature’ shows that Tween-80 has pro-inflammatory potential, leading to metabolic syndrome and promotes colitis and low-grade intestinal inflammation.[31]

From Traditional to Modern Medicine

Reflecting upon the information above – it is no wonder that turmeric has a long and safe history in disease prevention. Researchers are confirming the observations of our ancestors, thus inspiring health-conscious individuals. Isn’t it incredible that ancient knowledge dating back 4000 years, is suddenly validated by modern science? An advantage of knowing that turmeric has a long, safe and effective history is the additional bonus of turmeric compared to newer modern pharmaceutical products, such as the NSAIDs and associated anti-inflammatories with their well document gastric and hepatotoxicity. Moreover, we are able to better understand the mechanisms of action for how the whole spectrum of turmeric is an efficient ally for so many different diseases. As we have seen, inflammation is a common trigger for many diseases and turmeric shows significant anti-inflammatory, analgesic and anti-swelling potential.

From an Ayurvedic perspective, turmeric helps to balance all three dosha vāta, pitta and kapha, linking the dosha to pathophysiology we get the full picture: Inflammation = pitta-Aggravation, Pain = vāta Aggravation, Swelling = kapha Aggravation. Bringing all this together not only supports the benefits of turmeric with research but also links to the basic Ayurvedic principles simply observed in nature.
CONCLUSION
Ayurveda, the system of medicine originating in India, has survived as a distinct entity from remote antiquity until the present day. Turmeric’s history goes back over 2000 years, to the heyday of Ayurveda. Sushruta Samhita, dating to about 200 BCE, recommends a turmeric ointment to relieve the effects of consuming poisoned food and for wound healing. Today, turmeric is reaching new levels of awareness and respect. As is so often the case, extensive preclinical and clinical research on turmeric over the past few decades has confirmed most of its traditional uses. Modern medical findings include antioxidant, anti-inflammatory, anticancer, antigrowth, anti-arthritic, anti-atherosclerotic, antidepressant, anti-aging, antidiabetic, antimicrobial, wound healing, hepato-protective and memory-enhancing activities (which can be linked to its Ayurvedic actions described in the old texts of Charaka Saṃhitā. Turmeric is chemically diverse: so far approximately 235 compounds have been identified including polyphenolic, terpenes and volatile oils. Curcumin is just one compound that gives the yellow colour to turmeric. As the non-polar curcumin is poorly absorbed in water the other compounds in turmeric would have to be responsible for its potent pain relieving properties for which it was used. There are several reasons why we should consider using the whole spectrum of turmeric rather than only the pure curcumin: turmeric contains more than 200 bioactive compounds which are beneficial to your health. None of this goodness is present in any simple curcumin products. By taking isolated curcumin, you would forego the benefits of turmerones (part of the essential oil) which not only significantly enhances the absorption and transport of curcumin but are proven to exhibit anti-inflammatory and anticancer activities and support regeneration in neurologic disease.

Thus, it can be concluded that turmeric is a good example of herbal drug that can be proved that herbal drug should be used as wholesome to utilize all active principles of drug. However, there is need to carry out forward much efforts for utilizing optimum uses of herb using the sample of turmeric.

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