Curcumin bioavailability issues and its effect on birth defects

Abstract
The yellow pigment of turmeric (Curcuma longa) i.e. Curcumin (diferuloylmethane) has been associated with a number of properties such as antioxidant, anti-inflammatory, neurotrophic activity, antibacterial, antiviral, and anticancer etc. Oxidative stress is believed to be one of a major contributing factor for teratogenesis (congenital birth defects). However, enhanced oxidative stress may cause irreversible embryonic and foetal damage. However, Curcumin attracted attention due to its promising actions but limited bioavailability and inability to detect Curcumin in circulation or target tissues has causing hindered in the validation of a causal role. Here, we discuss the various scientific article enhance their activity by the improving their in intriguing form like nonparticle complex or with supplementation or in encapsulated form making its importance advance in the treatment of various ailments rather than congenital birth defects also.

Keywords: nonparticle, anticancer, congenital, bioavailability, foetal damage

Abbreviations: MTP, medical termination of pregnancy; AEDs, antiepileptic drugs; ROS, reactive oxygen species; THC, tetrahydrocurcumin; EE, encapsulation efficiency; CURMs; curcumin-loaded marinosomes; PLGA, polylactic-co-glycolic acid; FASD, fetal alcohol spectrum disorder

Introduction
Curcumin, obtained from rhizome of turmeric, is widely used as spice and food colouring agents, while also consume commonly in their diets by more than one billion people. Apart from kitchen uses, Ayurveda, Unani and Siddha system of medicines and in the Chinese medicines, uses of curcumin has been recommended for a wide range of disorders and diseases. In Ayurveda, its use has also been recommended for diverse medical indications such as wound healing, nausea, indigestion, inflammation, liver diseases, improving skin complexion and as an antioxidants etc. It has been reported by several workers, being an effective antioxidant, curcumin counteracts oxidative stress-induced damages by retrieving the situation of redox disequilibrium and thus recovering the activity of endogenous antioxidative defense system.

Since more than 50% of pregnancies are unplanned, sometimes the situation becomes crucial when a woman comes to know that she has to undergo treatment with some medication like epileptic drugs (might be a teratogenic) while she is pregnant and she is neither allowed undergoing for ‘Medical Termination of Pregnancy (MTP) nor keep the treatment pending until delivery.

Hence, it is now time to consider the priority of the situation and start research to develop medication regarding reduce the incidence and impact of birth defects. So, the products (natural or synthetic) which may have potential for helping to prevent birth defects among babies likely to be born from women taking any teratogenic drugs and also to allow the woman to continue with her unplanned pregnancy.

Discussion
Drug administration during the critical developmental period of development most of the time (in case of antiepileptic drugs (AEDs) i.e. valproic acid etc) produces toxic ROS by impairing glutathione homeostasis and induced birth defects. During gestation maternal circulation is directly linked to fetal circulation and the liver is the main site of drug metabolism hence, oxidative stress in the maternal system may induce oxidative stress in the foetuses which may cause fetotoxicity or embryotoxicity expressed in various ways including birth defects. Some investigators also suggest that, increased oxidative stress to the developing foetus imposed by the intermediate metabolites of drugs (AEDs) may be responsible for the teratogenic effects. They further added that as the embryonic and foetal antioxidant defence mechanisms are immature and develop slowly with the advancement in gestational age, enhanced oxidative stress may cause irreversible embryonic and foetal damage.

In several clinical studies have been carried out with Curcumin and also sowing the one of the major problems with Curcumin is perceived to be the bioavailability. However, the pharmacokinetics studies related to Curcumin from past three decades revealed its poor absorption and rapid metabolism that severely restrain its bioavailability activities. Forecast of its bioavailability revealed by the observation if showed its low serum levels, limited tissue distribution, apparent rapid metabolism and short half-life. In 1978, Wahlstrom and Blennow first revealed the uptake, distribution, and excretion of Curcumin in rat and found negligible amounts in blood plasma after oral administration of 1g/kg demonstrate it was poorly absorption from the gut. At higher dose of curcumin (2g/kg to rats orally) showed maximum concentration in serum is 1.35±0.23µg/ mL was observed at time 0.83 , whereas in humans the same dose of curcumin consequently in either undetectable or extremely low (0.006±0.0055µg/mL at 1h) serum levels. In a human clinical trial study, dosing of 3.6g of curcumin via oral route showed concentration in plasma 11.1nmol/L after an hour. So, the serum levels of curcumin
in rats and in human are very much deferent. Whether curcumin metabolites are as active as curcumin itself is, unfortunately, not clear. Many studies point out that curcumin metabolites glucuronides and tetrahydro curcumin (THC) are less active than curcumin itself. The stability of Curcumin is observed by their half-life existence in the body. However, systemic elimination or clearance from the animal system determines its relative biological activity but unfortunately earlier study reported that when Curcumin was given orally 1g/kg to rats then approximately seventy five percent of it was excreted in the feces and insignificant amounts were noted in the urine. Although, now in the fast growing technology and science the drug delivery system of the chemical molecule now modified and enhancing their properties by the supplementation of additives along them that potentiate their effects.

Micronized of the Curcumin in a PTZ-induced seizure model in zebrafish (Danio rerio) through supercritical carbon dioxide processing, a suitable green chemistry technique to prepare and modify material properties. The results showed very promising protective effects, slowing seizure development both in larvae and adult animals. Recent article revealed that the Curcumin-loaded marinosomes (CURMs - encapsulated in krill lipids-based liposomes) showed a powerful antioxidant activity to develop a potential anticancer therapy from low-cost and readily available nutreacuticals. Reflux followed by thin drug-lipid film method is used successfully to incorporate the drug into the liposomal membrane at high encapsulation efficiency (EE). These new CURM techniques showed as a favorable in vitro drug delivery system to target cancer disease. To improve curcumin bioavailability, polyelectrolyte complexation method to form layer-by-layer assembled nanoparticles, for curcumin delivery, negatively charged acylated cruciferin (ACRU), a rapeseed globulin. The studies suggested that improved permeability efficiency of free curcumin through the Caco-2 cell monolayer and these ACRU/CS NPs can be used for encapsulation and delivery of curcumin in functional foods also. The other effective formulation that enhance the bioavailability of Curcumin by Polylactic-co-glycolic acid (PLGA) encapsulated Curcumin nanoparticles, curcumin-beta-cyclodextrin nanoparticle, and in humans, curcumin bioavailability was huge increased by about 2,000% at 45 minutes after co-administering of the Curcumin orally along with piperine.

Although, Curcumin has been known as a potent scavenger of reactive oxygen species (ROS), which enhances the activity of antioxidants properties by suppresses phosphorylation of transcription factors involved in inflammation and apoptosis in the tissues. The Curcumin containing turmeric extract rescues ethanol-induced developmental defect in the zebrafish model for fetal alcohol spectrum disorder (FASD) which was due to ethanol-induced oxidative stress as reported. In another study, Curcumin reduces high glucose-induced NTD formation by blocking cellular stress and caspase activation, suggesting that curcumin supplements could reduce the negative effects of diabetes on the embryo.

Conclusion

Use of Curcumin since ancient times has been used against human ailments in Asian countries. Now modern science has delineated the molecular basis in advance form for their use. Various formulations of Curcumin that are currently available are also discussed here. However daily going research will go to improve the bioavailability of Curcumin, via development of new strategies through the modification of the modulation of route administration and complexes and structural modifications of Curcumin. Therefore, further investigation will be needed to determine by the experimental findings because of its great medicinal value for human being.

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Conflict of interest

The authors declare that there is no conflict of interests regarding the publication of this paper.

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