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Review

Pharmacokinetic interactions of curcuminoids with conventional drugs: A review

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ABSTRACT

Ethnopharmacological relevance: Herb–drug interactions are of great concern in health practices. Curcumin is a natural polyphenol extracted from turmeric, a spice widely used all over the world. Curcumin is clinically used due to its acceptable safety profile and therapeutic efficacy.

Aim of the study: Current paper aims to highlight the effect of curcumin on concomitantly used drugs.

Methods: Electronic databases including PubMed, Scopus and Science Direct were searched with the keywords "curcumin" in the title/abstract and "drug interaction," "drug metabolism," "cytochrome," "P-glycoprotein" and "P450" in the whole text.

Results: Curcumin can induce pharmacokinetic alterations such as changes in C_{max} and AUC when concomitantly used with pharmacological agents like cardiovascular drugs, antidepressants, anticoagulants, antibiotics, chemotherapeutic agents, and antihistamines. The underlying mechanisms of these interactions include inhibition of cytochrome (CYP) isoenzymes and P-glycoprotein. There is only one clinical trial which proved a significant alteration of conventional drugs in concomitant use with curcumin indicating the need for further human studies.

Conclusions: Although *in vitro* and *in vivo* studies do not provide enough evidence to judge the clinical drug interactions of curcumin, physicians must remain cautious and avoid drug combinations which may lead to curcumin-drug interactions.

1. Introduction

Herb-drug interactions, which may result in an increase in side effects and a decrease in pharmacological efficacy, are one of the main concerns in health practices. Conventional drugs (shortly mentioned as "drugs") are defined as substances used for diagnosis, prevention, or treatment of diseases (https://www.merriam-webster.com/dictionary/drug). Most of the currently available drugs originate from natural sources which underwent chemical modifications to improve their safety and efficacy. On the other hand, herbal medicines are herbal preparations containing plant materials or purified/fractionated botanical extracts which are used in their natural form (http://www.who.int/medicines/areas/traditional/definitions/en/) and are usually provided as supplements. Natural products are administered as an adjunct to conventional drugs or as an alternative treatment; however, when concomitantly used with conventional drugs, the likelihood of pharmacokinetic interactions is increased (Hyodo et al., 2005; Hung et al., 2015; Srinivas, 2015; Siah et al., 2016).

Turmeric, the dried or fresh rhizome of *Curcuma longa* L. from the family Zingiberaceae, is an ancient medicinal plant most notably used in gastrointestinal disorders, malignancies and inflammatory conditions (Prasad and Aggarwal, 2011). Despite the presence of several phytochemicals such as tumerone and different polysaccharides (Tohda et al., 2006; Funk et al., 2010), turmeric mostly owes its therapeutic activities to a group of yellow pigments known as curcuminoids. Curcuminoids are a mixture of curcumin or diferuloylmethane (IUPAC name: (1E, 6E)-1,7-bis (4-hydroxy-3-methoxyphenyl) hepta-1,6-diene-3,5-dione) (Pubchem.com/curcumin) as the major compo-

Abbreviations: OTC, over the counter; AUC, area under the plasma concentration-time curve; AUMC, area under first moment of plasma drug concentration-time curve; MRT, mean residence time; $V_d$area, apparent volume of distribution; CL, clearance; CYP, cytochrome; P-gp, P-glycoprotein; C_{max}, maximum plasma concentration; ka, absorption rate constant; OATP, organic anion transporting polypeptide

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nent, as well as small amounts of demethoxycurcumin and bisdemethoxycurcumin (Lestari and Indrayanto, 2014).

Today, curcumin is a well-known phytochemical with several biological activities such as antioxidant, anti-inflammatory (Menon et al., 2007, Farzaei et al., 2015b), anti-ulcer (Farzaei et al., 2015a), anticancer (Aggarwal et al., 2003; Hosseinzadeh et al., 2011; Farzaei et al., 2016), antimicrobial (Moghadamtousi et al., 2014), wound healing (Akbik et al., 2014) and hepatoprotective properties (Vera-Ramirez et al., 2013), as well as beneficial effects in neurodegenerative and psychological disorders (Bahramsoltani et al., 2015; Shahpiri et al., 2016). Furthermore, there are newly discovered pharmacological activities for curcumin in cardiovascular disorders like myocardial ischemia/reperfusion injury, arrhythmia, and hypertrophic cardiomyopathy (Jiang et al., 2017), eye diseases such as conjunctivitis, corneal diseases, pterygium, cataracts and glaucoma (Liu et al., 2017) and diabetic cardiomyopathy, a multifactorial condition which causes high mortality rates in diabetic patients (Karuppagounder et al., 2017). Curcumin is one of the few phytochemicals which shows acceptable safety and a wide therapeutic index for clinical use in purified form (Farzaei et al., 2016). In the field of oncology, curcumin has strengthened its foothold as a part of antioxidant therapy in the treatment of several cancers (Anand, 2008). A recent review suggested curcumin could modulate several side effects of chemotherapy-induced toxicities such as nephrotoxicity and neurotoxicity (Rezaee et al., 2017). There are also clinical trials which have demonstrated the antidepressant activity of curcumin in humans (Bahramsoltani et al., 2015). Furthermore, a recent meta-analysis confirms the effectiveness of curcumin as a well-tolerated natural treatment in depression (Ng et al., 2017).

Similar to conventional drugs, natural agents are capable of causing drug-drug interactions with other classes of medicines which may be lethal and lead to lower effectiveness and/or increased toxicity. As a widely-used over the counter (OTC) herbal antidepressant, St. John's wort significantly alters the pharmacokinetics of concomitantly used oral contraceptives, immunosuppressives, lipid lowering agents, antihypertensive drugs, and chemotherapeutic agents (Rahimi and Abdollahi, 2012). Some medicinal plants such as Ginkgo and garlic have been known to cause uncontrollable bleeding when used together with warfarin. Ginseng (*Panax ginseng*) is reported to induce mania in patients under antidepressant therapy (Fugh-Berman et al., 2000). Echinacea, kava (*Piper methysticum*) and saw palmetto (*Serenoa repens*) are other examples of medicinal plants in which significant clinical drug interactions have been observed (Izzo and Ernst, 2001). A recent review by Choi et al. (2016) reported an increase in the number of herb-drug interactions, especially pharmacokinetic interactions (Choi et al., 2016). Another study on the herb-drug interactions amongst patient with cardiovascular disorders proposed cytochrome P450 (CYP450) and other drug transporters as main pathways underlying pharmacokinetic alterations of conventional drugs in concomitant use with herbal supplements (Wang, 2015). Several papers reported reduced efficacy of warfarin, cyclosporine, antihyperglycemics, oral contraceptives, and neurological drugs, as well as increased adverse effects of conventional drugs like gastrointestinal bleeding, liver damage and hypoglycemia, as a result of these herb-drug interactions (Choi et al., 2016)

Increasing the clinical importance of curcumin leads to essential assessments regarding its drug interactions. Thus, the present study aims to summarize current literature regarding curcumin interactions with conventional drugs.

2. Method and search strategy

Electronic databases including PubMed, Scopus and Science Direct, were searched with the keywords "curcumin" in the title/abstract and "drug interaction," "drug metabolism," "cytochrome," "P-glycoprotein," "pharmacokinetic" and "P450" in the whole text. Results were collected from the year 1966 until October 2016. Inclusion criteria were *in vitro*, *in vivo* or clinical evaluations of purified curcuminoids or turmeric extracts on the pharmacokinetics of conventional drugs or activity of CYP, P-glycoprotein (P-gp) and other drug-metabolizing enzymes as well as transporters, papers with available full-texts, and English full-texts. Exclusion criteria were the mixture of curcuminoids with other herbal or non-herbal materials, assessments on the pharmacological activity of curcumin without concomitant therapy with other drugs and/ or without evaluating the changes in the pharmacokinetics of the conventional drugs, review articles, papers with non-English full-texts and papers without available full-text. Primary search results were screened by two independent investigators. Data from the final included articles were summarized in two tables representing *in vitro* and *in vivo*/ clinical studies.

3. Mechanisms underlying drug interactions of curcumin

From the total of 5784 primary results, 2264 were duplicates, 4 were excluded because the full-texts were not in English, 41 because they were review articles and 3407 were excluded based on the title/ abstracts. A total of 68 papers were screened based on their full-texts, and 35 were excluded since they did not meet the inclusion criteria. Finally, 33 papers were included in this study.

The most assessed mechanisms were the pharmacokinetic changes through CYP450, followed by P-gp, along with a fewer number of investigations on organic anion-transporting polypeptide (OATP), glutathione-S-transferase (GST) and uridine dinucleotide phosphate glucuronosyltransferases (UDPG) (Fig. 1).

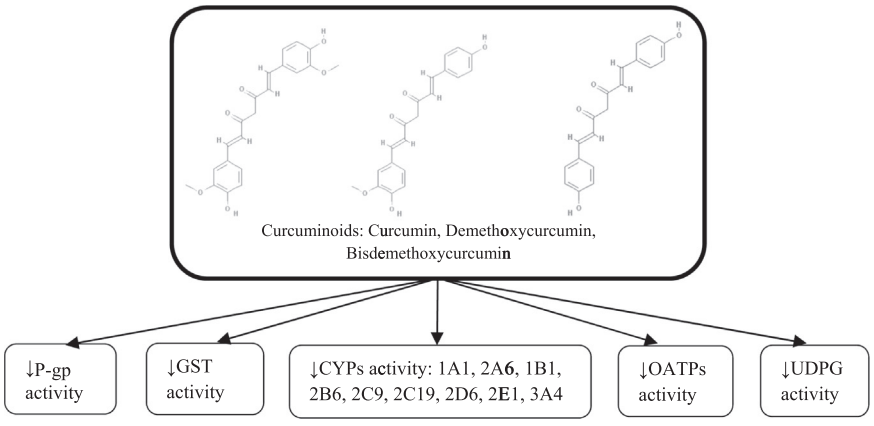

Fig. 1. Pharmacokinetic interactions of curcumin with other drugs. CYP: cytochrome P450, CL: clearance, OATP: organic anion-transporting polypeptide, AUC: area under the plasma concentration-time curve, C_{max}: maximum plasma concentration, GST: glutathione-S-transferase, P-gp: P-glycoprotein, UDPG: Uridine dinucleotide phosphate glucuronosyltransferases.