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Intranasal curcumin and its evaluation in murine model of asthma

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ABSTRACT

Curcumin, a phytochemical present in turmeric, rhizome of *Curcuma longa*, has been shown to have a wide variety of pharmacological activities including anti-inflammatory, anti-allergic and anti-asthmatic properties. Curcumin is known for its low systemic bioavailability and rapid metabolization through oral route and has limited its applications. Over the recent decades, the interest in intranasal delivery as a non-invasive route for drugs has increased as target tissue for drug delivery since nasal mucosa offers numerous benefits. In this study, we evaluated intranasal curcumin following its absorption through nasal mucosa by a sensitive and validated high-performance liquid chromatography (HPLC) method for the determination of intranasal curcumin in mouse blood plasma and lung tissue. Intranasal curcumin has been detected in plasma after 15 min to 3 h at pharmacological dose (5 mg/kg, i.n.), which has shown anti-asthmatic potential by inhibiting bronchoconstriction and inflammatory cell recruitment to the lungs. At considerably lower doses has proved better than standard drug disodium cromoglycate (DSCG 50 mg/kg, i.p.) by affecting inflammatory cell infiltration and histamine release in mouse model of asthma. HPLC detection revealed that curcumin absorption in lungs has started after 30 min following intranasal administration and retained till 3 h then declines. Present investigations suggest that intranasal curcumin (5.0 mg/kg, i.n.) has effectively being absorbed and detected in plasma and lungs both and suppressed airway inflammations at lower doses than the earlier doses used for detection (100–200 mg/kg, i.p.) for pharmacological studies (10–20 mg/kg, i.p.) in mouse model of asthma. Present study may prove the possibility of curcumin as complementary medication in the development of nasal drops to prevent airway inflammations and bronchoconstrictions in asthma without any side effect.

1. Introduction

Asthma is one of the most common chronic inflammatory diseases. As per latest report from World Health Organization, about 300 million people worldwide have suffered from asthma [1]. It is characterized by airway inflammation, with intermittent episodes of wheezing and coughing [2,3]. Inhaled corticosteroids provide one of the most effective therapies, but this method has severe side effects after long-term use [4,5] such as hypertension, cataracts, osteoporosis in elderly patients and stunted growth in children. However, inhaled corticosteroids are still required in the systemic administration of glucocorticoides for intractable asthma [6,7].

It is well established that mast cells play a key role in the pathogenesis of allergic diseases including asthma [8,9]. Mast cells participate in airway inflammation by IgE-receptor (FcεRI) cross-linking with exposed antigen, secreting variety of pro-inflammatory mediators including histamine, serotonin, eicosanoides and platelet activating factors as well as various cytokines and chemokines [10–12]. Among the released mediators, histamine from mast cells and peroxidases (EPO) released from eosinophils are one of the most important chemical mediators in the allergic reactions, which are responsible for airway constriction leading to difficulty in breathing. Another most striking feature is the accumulation of large number of inflammatory cells in perivascular and peribronchial region of the lung parenchyma. These inflammatory cells include lymphocytes, macrophages, neutrophils with strikingly large number of eosinophils. Local allergen challenge in patients with bronchial asthma [13], allergic conjunctivitis [14] and atopic dermatitis [15] has been shown to result in rapid elevation of prostaglandin D2 (PGD2) level in nasal and bronchial lavage fluids, tears and skin chamber fluids. PGD2 is the major cyclooxygenase metabolite produced by mast cells responding to IgE-dependent stimuli [16].

Recent years have seen the development of highly targeted biological treatment and synthetic therapies with some serious side effects. Natural medicines obtained from plants have been used in

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therapeutics from ancient times as these have the benefit to have minimal toxicity. Thus, natural treatments as complementary medicines have drawn the attention of the scientific community to ancient remedies. Curcumin, a phytochemical present in turmeric, the rhizome of *Curcuma longa*, has been shown to have a wide variety of pharmacological activities including anti-allergic and anti-inflammatory properties [17]. Curcumin [1,7-bis(4-hydroxy-3-methoxyphenyl)-1,6-heptadien-3,5-dione], being a phenolic substance, is used as a dietary spice and natural colouring agent for foods. Its yellow colour is imparted primarily by curcumin (diferuloyl methane) and polyphenolic pigment [18]. In recent years, it has attracted interest because of its antioxidant, anti-inflammatory and potential cancer chemopreventive activities [19]. Studies have suggested that curcumin has downregulated Th2 responses and reduced lung inflammation in latex sensitized mice suggesting possible role of curcumin in controlling allergic disorders [20,21].

In common with several other diet-derived polyphenols, curcumin has low systemic bioavailability [22]. This pharmacokinetic feature of curcumin, which has been observed across several species, is the result of poor absorption and avid metabolic conjugation and reduction [23]. Despite the evidence that curcumin is poorly available following oral administration, there are reports that curcumin at 50–200 mg/kg doses exerts biological activity on sites distant from the locus of absorption in rodents, such as breast [24–26], prostate, lung and especially the liver [27–29]. Studies on gall bladder contractility following oral curcumin in humans suggest that curcumin may exert biological actions at doses of 20 mg [30–33].

Several studies have suggested poor bioavailability of curcumin in both rodents and humans despite the promising biological effects that have been observed (Fig. 1) [34,35]. Pan et al. [36] investigated the pharmacokinetic properties of curcumin administered either orally or intraperitoneally (i.p.) in mice. With oral administration of 1.0 g/kg of curcumin, low plasma levels of 0.13 μg/ml appeared after 15 min, while a maximum plasma level of 0.22 μg/ml was obtained at 1 h; plasma concentrations declined then below detection limit by 6 h. Entirely different plasma curcumin levels were found after i.p. administration of 0.1 g/kg. Plasma curcumin levels peaked (2.25 μg/mL) within 15 min of administration and declined rapidly within 1 h. An investigation reported that it was difficult to detect curcumin in plasma following 180 mg oral dose [35]. Poor absorption through oral route could be due to its extremely low aqueous solubility and/or extensive pre metabolism [37]. Earlier studies reported that nasal cavity may be exploited as a route of entry into systemic circulation since nasal mucosa is highly vascular and increases the absorption of the drug [38,39].

Curcumin is unstable at neutral and basic pH values and is degraded to ferulic acid ([4-hydroxy-3-methoxycinnamic acid]) and feruloylmethane (4-hydroxy-3-methoxycinnamoyl-methane) [34]. In the course of investigations, it was found that more than 90% of curcumin decomposes rapidly in buffer systems at neutral basic

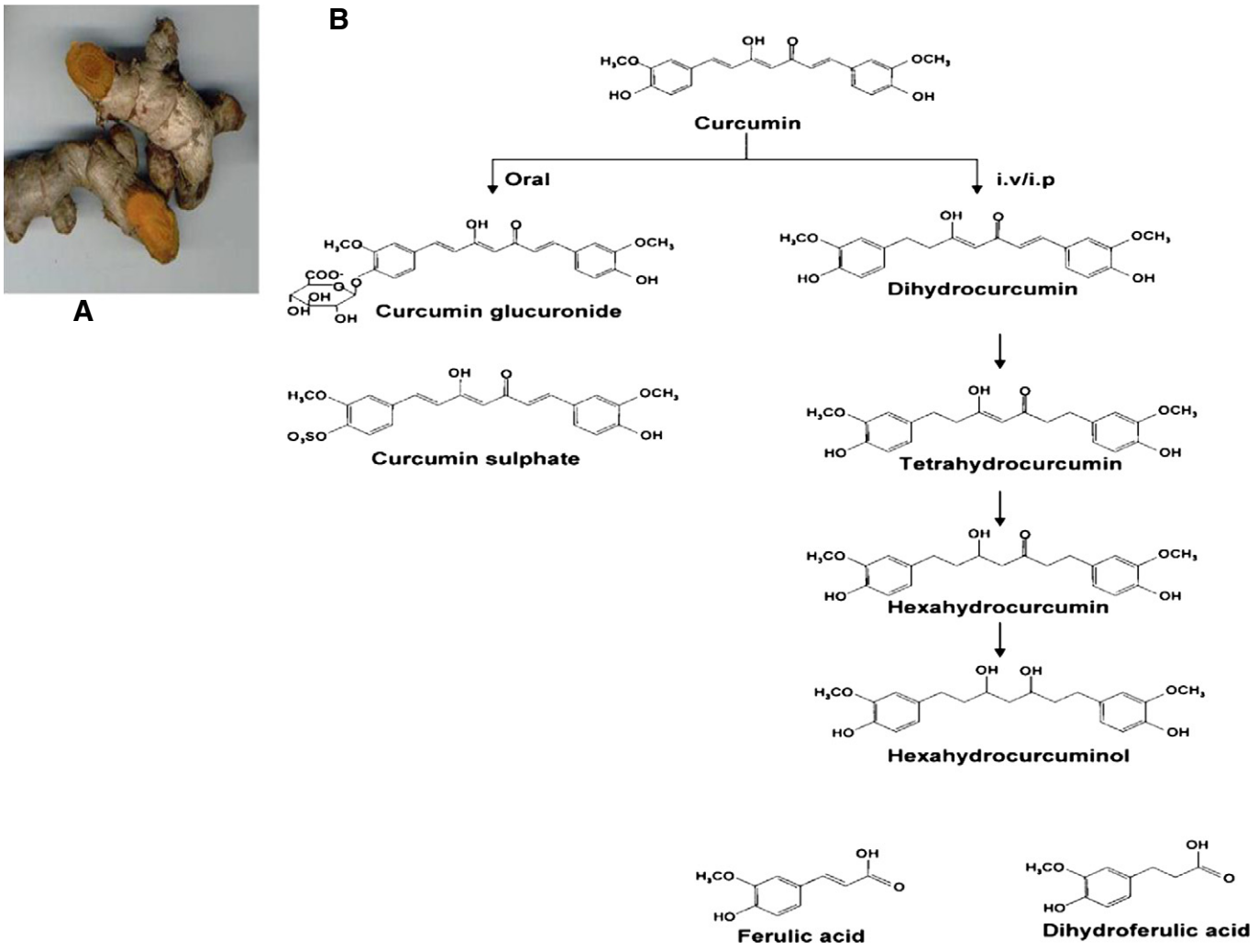

Fig. 1. (A) Rhizome of curcumin. (B) Structure and its metabolites (Anand et al. [34]).