Ginger

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Ginger in its many forms, from juices of the fresh rhizome, to ginger powder and ginger essential oil, is growing in popularity for claimed universal health benefits. Nevertheless, and contrarily to the common notion of the public, ginger is not devoid of side effects, especially interactions with other drugs, and many of the claimed benefits remain to be substantiated.

Keywords: bioavailability ; medication interactions ; clinical trials ; encapsulation ; nano-carriers

1. Introduction

1.1. Ginger in History and in the Present Day

Ginger is long known to man. Its history dates back over 5000 years when the Indians and ancient Chinese cultivated it as a tonic root for all ailments. The plant, of scientific name *Zingiber officinale*, is originally from southern parts of ancient China and from there it spread to India, Maluku Islands (so-called Spice Islands), the rest of Asia and West Africa. Ginger first appeared in Europe in the 1st century, from Roman trade with India. It was extensively used by the Romans, falling out of use during the middle ages [1]. Ginger has been used, since old times, in a variety of traditional medicines, including Chinese, Ayurvedic (from India) and Unani (Perso-Arabic) [2]. In the ayurvedic tradition, ginger is considered a universal medicine, but it is used with stronger incidence in the treatment of nausea and indigestion [3].

In the present day, ginger is used both in food and as a herbal medicine. The World Health organisation (WHO) monograph on ginger compiles the results on anti-emetic, cholagogic and anti-inflammatory properties available in a variety of sources, including the pharmacopeias of Japan, China, Thailand, UK, Europe and Africa [4]. In food, ginger is most commonly used as a spice. The rhizomes are dried and ground to a powder that has flowery-spicy taste and aroma. Both ginger spice and ginger essential oil are recognised as food additives by the US Food and Drug Administration (FDA) and they have been granted the GRAS status (“Generally Recognised as Safe”) [5]. Other ginger-derived food products include ginger pickles, ginger preserves, ginger beer and juices made from fresh ginger. Candied ginger is eaten *per se* or incorporated into chocolates and confectionery. Various extracts are added to yogurt and other dairy products. The use of ginger as a dietary supplement and functional food is a growing trend. Ginger is one of top-selling herbs in the market, estimated to have an annual sales growth of 6.5% and to reach a value 4.18 billion UD dollars by 2022. The consumers’ market is predicted to expand even faster, at an estimated rate of 7.5% every year until 2022 [6].

1.2. Ginger Chemistry

Ginger contains starch as the most abundant ingredient, making 40–60% (m/m) of the dry rhizome. The contents in protein, lipids and fiber vary according to the cultivars and the different maturity stages: the percentage of the crude protein is 6.2–19.8%, lipids 5.7–14.5% and crude fibers 1.1–7.0%. The active components are obtained by extraction. This process can be done using organic solvents that, once dried, afford the oleoresin in yields of 4–7.5% (m/m), or by steam distillation that affords obtain ginger oil [7]. The extracts contain a large variety of compounds, of which at least 115 have already been identified and that include gingerols, shogaols, β-carotene, capsaicin, caffeic acid, curcuminoids and salicylate [8]. Gingerols are the most abundant active components in fresh ginger, whereas in dry ginger the shogaols are more abundant; this happens because the heat associated with drying degrades gingerols into shogaols [9]. The family of gingerols is quite extensive, with up to 31 identified in fresh ginger so far [10]. Besides 4-, 6-, 8-, and 10-gingerols, as well as 6- and 14-shogaols, a number of other bioactive components are known, mainly for their anti-inflammatory activity; these include methoxy-10-gingerol, 10-gingerdione, 1-dehydro-10-gingerdione, hexahydrocurcumin, tetrahydrocurcumin, and gingerenone A (Figure 1) [11][12].

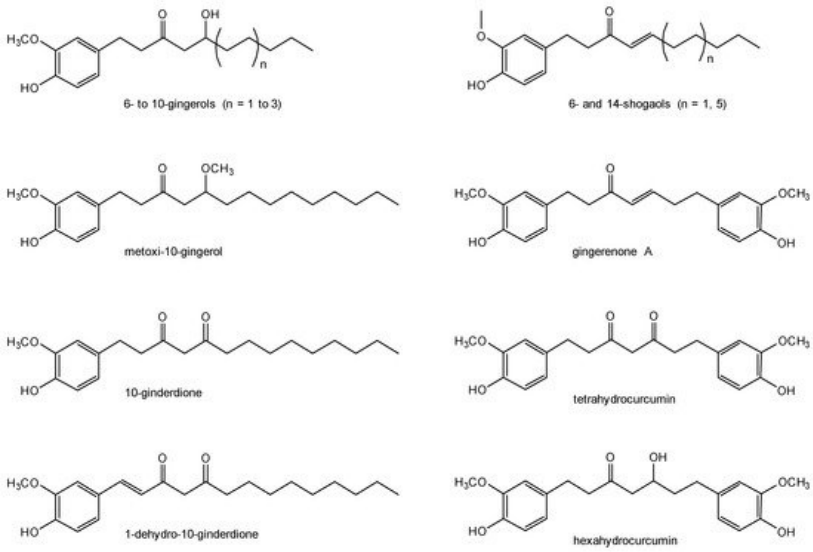

Figure 1. Structural representation of the most relevant bioactive compounds occurring in ginger.

6-gingerol, with the IUPAC name (S)-5-hydroxy-1-(4-hydroxy-3-methoxyphenyl)-3-decanone, is the main pungent and bioactive component of ginger. 6-gingerol is soluble in ethanol, benzene, ether, chloroform, methanol (1 mg/mL), and DMSO and insoluble in water. The log P of 6-gingerol is predicted to lie between 2.48 and 3.62, and it has been provisionally categorised as a BCS class I compound, that is, a compound with low solubility and low permeability (BCS stands for Biopharmaceutical Classification System) [13]. Extraction of 6-gingerol is usually carried out by chromatographic purification of extracts obtained by maceration of fresh ginger with different solvents like methanol [14], hexane [15] or acetone. The yields of these processes are, however, very low, lying between 0.1 and 0.6%. Furthermore, the use of organic solvents makes the product inadequate for food applications. Attempts to obtain gingerol with supercritical CO_2 [16] [17] and subcritical water [18] are reported, but these methods afford, rather than pure 6-gingerol, a mixture of 6, 8- and 10-gingerols, as well as 6-shogaol. Pure 6-gingerol can be obtained by total synthesis, involving more than ten steps and various precursors [19].

2. Pharmacology of Ginger

2.1. Pharmacokinetics from Oral Intake

The amount of ginger active components that reach the bloodstream following oral intake is relatively low due to losses during gastroenteric absorption. Furthermore, gingerols, like most orally administered apolar phenolic compounds, undergo glucuronide and sulfate conjugation that takes place primarily in the intestinal mucosa and secondarily in the liver and other tissues [20]. This way, plasma components of ginger are typically found in the conjugated forms rather than the free ones. This was demonstrated by a study on mice treated with 250 mg/kg of ginger extract. The study monitored the main active components of ginger in the free form, revealing very low seric levels [21]. Also remarkable are the different absorption kinetics observed for each one of the components. The 6-gingerol plasma peak was observed at roughly two hours of administration (but with a large error, 27.18 ± 38.43 µg/L), while 10-gingerol peaked at 30 min (55.95 ± 31.61 µg/L) and 8-gingerol was practically undetected; 6-shogaol peaked at 10 min with only 4.04 ± 5.37 µg/L.

Pharmacokinetics of ginger in humans was investigated using an escalation study with 27 healthy subjects. A single oral dose of ginger extracts was administered, with concentrations standardised to 5% of total gingerols and ranging from 100 mg to 2.0 g. The subjects were monitored for 6-, 8-, 10-gingerols and 6-shogaol [22]. The compounds were rapidly absorbed, with a t_{max} of 55 to 65.6 min (range: 45–120 min) and elimination half-lives ($t_{1/2\beta}$) of 75 to 120 min at the highest dose, 2.0 g. No free 6-, 8-, 10-gingerols or 6-shogaol were observed in the plasma, in agreement with the studies performed with mice. Instead, their circulating metabolites were detected, mostly glucuronides and/or sulphates (Table 1).

Table 1. Pharmacokinetic parameters for the main active components of ginger.

Component	Dose (mg)	C_{max} (μg/mL)	AUC (μg·min·mL^{-1})	t_{max} (min)	$t_{1/2\beta}$ (min)
6-gingerol, total	1000	0.4 ± 0.2	12.6 ± 6.4	55.0 ± 7.7	—
	1500	1.69 ± 2.31	75.6 ± 110.3	60.0 ± 0.0	—
	2000	0.85 ± 0.43	65.6 ± 44.4	65.5 ± 22.6	110.0 ± 34.9
6-gingerol glucoronide	1000	0.16 ± 0.15	—	—	—
	1500	0.62 ± 0.62	—	—	—
	2000	0.62 ± 0.56	—	—	—
6-gingerol sulphate	1000	0.02 ± 0.03	—	—	—
	1500	0.04 ± 0.04	—	—	—
	2000	0.33 ± 0.41	—	—	—
8-gingerol, total	1000	0.1 ± 0.1	2.1 ± 2.2	52.5 ± 8.7	—
	1500	0.1 ± 0.1	2.6 ± 2.0	60.0 ± 0.0	—
	2000	0.23 ± 0.16	18.1 ± 20.3	73.1 ± 29.4	113.5 ± 41.1
10-gingerol, total	1000	0.1 ± 0.1	2.9 ± 3.2	60.0 ± 0.0	—
	1500	0.1 ± 0.02	7.7 ± 5.3	80.0 ± 34.6	—
	2000	0.53 ± 0.4	50.1 ± 49.3	75.0 ± 27.8	128.7 ± 38.8
6-shogaol, total	1000	0.1 ± 0.1	0.8 ± 1.5	55.0 ± 8.7	—
	1500	0.4 ± 0.08	1.6 ± 2.8	60.0 ± 0.0	—
	2000	0.15 ± 0.12	10.9 ± 13.0	65.6 ± 22.6	120.4 ± 42.0

Note: C_{max} = maximum plasma concentration, AUC = area under the concentration-time curve, t_{max} = time point at which C_{max} is observed, $t_{1/2\beta}$ = elimination half-life.

It should be noted that only 6-gingerol conjugates were detectable in subjects taking doses below 1.0 g, and for this reason, the low doses are not listed in the Table 1. The AUC values for the doses of 250 and 500 mg of ginger presented low values, of 2.8 and 5.3 μg·min·mL^{-1} respectively. For the two lowest doses of ginger tested, 100 and 250 mg, the Cmax of 6-gingerol conjugates had values of 0.3 and 0.4 μg/mL, respectively. Ginger was well tolerated in all subjects.

Ginger metabolism and excretion is still not fully determined. Studies using 6-gingerol as a model show that this molecule is extensively metabolised in the liver by enzymes of the uridine diphosphate glucuronosyltransferase family to form glucuronide conjugates [20][23]. Roughly, half of the administered 6-gingerol is excreted through the bile as a glucuronide, with only 2–3% appearing in the urine in the free form [20]. Other metabolites, formed by hepatic oxidation and eliminated

in the urine, include 9-hydroxy-6-gingerol, vanillic acid, ferulic acid, (S)-(+)-4-hydroxy-6-oxo-8-(4-hydroxy-3-methoxyphenyl)octanoic acid, and 4-(4-hydroxy-3-methoxyphenyl)butanoic acid.

2.2. Safety and Interactions

Ginger is a very safe herbal medicine, able to be used even in pregnancy [24][25]. Nevertheless, it is not completely free from side effects and it also displays a long list of interactions with other compounds, from pharmaceutical active ingredients (APIs) to vitamins and nutrients. In these interactions, ginger acts mostly as a bioenhancer, that is, an agent that enhances the bioavailability of other substances. This effect may be associated with the presence of piperine-like compounds in ginger [26]. Piperine, the pungent compound in black pepper, is a well-known bioenhancer. However, ginger interactions with APIs are not fully predictable and reduction of bioavailability is also reported.

2.3. Biological Activity

Ginger is indicated in Ayurvedic, Chinese and Unani traditional medicines for a large variety of pathologies and ailments, often being considered a panacea or universal medicine. Most of this knowledge is, however, empirical, and only in the latest decades has clinical trial-based evidence been gathered on the activities of ginger.

3. Encapsulation of Ginger

3.1. Dispersion and Micronisation

Encapsulation of ginger essential oil or ginger oleoresin by forming a dispersion into a polymer or other carrier agent, with subsequent drying and micronisation (commonly in one step, by spray-drying), is a common solution for the protection of the active ingredients against volatilisation or against degradation by heat and light. In addition, liquid and semi-solid extracts are turned into powdered solids which are easier to store and handle.

In the case of ginger essential oil, encapsulation can be achieved with various agents including inulin, whey protein (WP) [27] and a WP/maltodextrin blend [28]. For ginger oleoresin, various methods and dispersing agents are described by Janayudin et al. [29], including chitosan and blends of maltodextrin with caseinate or arabic gum. Chitosan [30] and chitosan-alginate mixtures [31] can also be used to form microcapsules with the oleoresin of red ginger, a subspecies of ginger containing higher amounts of 10-gingerol, 6-gingerdiol and its acetylated derivatives [32].

3.2. Liposomal Ginger

Some liposomal ginger products are available on the market, namely a combination of ginger, curcumin and docosahexaenoic acid (an omega-3 fatty acid) named ‘Micelle Liposomal Curcumin Gold’ [33] and another comprising turmeric, lemon and ginger, called ‘Synchro Gold Lemon Ginger’ [34]. Inclusion of a lipophilic drug into liposomes aims usually at increasing its bioavailability, which, in the case of the two marketed herbal supplements, would refer to oral absorption, given that these are to be taken by this route. Nevertheless, to the best of our knowledge, the effect of liposomes on the oral bioavailability of the active components from ginger remains yet to be demonstrated by any in vivo studies or clinical trials.

Available research into the benefits of liposomes for ginger biotechnological applications includes the evaluation of stability and dermal bioavailability. Inclusion of ginger extract into nanoliposomes was shown to help preserve its antioxidant properties [35] and its skin permeability, measured on an in vitro goat skin model [36].

4. Novel Drug Delivery Technologies Based on Ginger

4.1. Ginger-Derived Nanoparticles (GDPs)

Fresh ginger juice can be used to afford, by a controlled methodology [37][38][39], ginger-derived nanoparticles (GDPs) that are suitable for loading and carrying APIs or other compounds. GDPs from ginger contain lipids, mainly phosphatidic acids (41.9% of total lipids), digalactosyldiacylglycerol (27.4%) and monogalactosyldiacylglycerol (18.9%) [40], as well as a fair amount of RNA [39]. GDPs have, thus, an intrinsic immunomodulatory activity, inducing production of the cytokines IL-6 and IL-10 when incubated with macrophages. Furthermore, they are not destroyed in the stomach [39], and they are able to enter liver cells (hepatocytes) in mice [41], where they demonstrated a protective effect against alcohol-induced liver damage.

The high biocompatibility of GDPs and their ability to easily fuse with biological membranes owing to the high content in phosphatidic acids makes them excellent candidates for innovative biological therapies. Chronic diseases associated with

genetic dysfunction, such as ulcerative colitis, can be treated by gene therapy or by knocking out a target gene using small interfering RNAs (siRNAs). SiRNAs are small double-strand sequences able to knock down specific genes, in this case CD98. GDPs loaded with siRNA-CD98 were tested both in vitro and in vitro as an innovative therapy for ulcerative colitis. In vitro studies on the RAW 264.7 and colon-26 cell lines show successful transfection, with distribution of the GDPs throughout the cells and inhibition of the expression of CD98 gene by roughly 20% in colon-26 cells and 50% in RAW cells. The GDPs have also good distribution in vivo, with studies on mice demonstrating that they have a preferential action (CD98 knock-out) on the ileum and the colon [40].

4.2. Ginger-Derived Nano-Vectors (GDNVs)

GDPs can be transformed into other kinds of carriers by extracting the lipids they contain and leaving the RNA behind. The extracted lipids form, by sonication, nano-sized vesicles that received the acronym of GDNVs. These new carriers are taken up by intestinal cells, as demonstrated in vitro on the Colon-26 and HT-29 human colon adenocarcinoma cell lines, and biocompatible as demonstrated by the lack of toxicity in vivo on mice. Furthermore, they act effectively as carriers for oral administration of the antitumoral drug doxorubicin and this therapy successfully inhibited tumor growth in a Colon-26 xenograft tumor mouse model [42].

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