Journal of Herbal Medicine 5 (2015) 184–189

Contents lists available at ScienceDirect

Journal of Herbal Medicine

journal homepage: www.elsevier.com/locate/hermed

Research paper

Clinical evaluation of the anti-sweet effects of *Gymnema sylvestre* extract developed into a dispersable oral tablet

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ARTICLE INFO

Article history:
Received 25 March 2015
Received in revised form 18 June 2015
Accepted 21 September 2015
Available online 28 September 2015

Keywords:
Anti-sweet
Gymnema sylvestre
Herbal formulations
Oral dispersing tablets
Taste masking

ABSTRACT

Aim of the study: Gymnema sylvestre is a well-known herb noted for its anti-sweet and antidiabetic properties in both traditional and Ayurvedic medicine. The use of modern phyto-pharmaceutical methods may be used to improve both the palatability and efficacy of herbal medicines previously prepared using old traditional methods. The aim of the present study was to develop an improved formulation of *G. sylvestre* extract that utilized its anti-sweet properties for diet control in obesity with the added advantage of being patient compliant.

Materials and methods: The anti-sweet dosage forms of *G. sylvestre* extract were prepared as oral dispersing tablets for immediate action. The bitter and unpleasant taste of the plant was masked to improve its palatability. The formulation developed was clinically evaluated for bitter taste masking and anti-sweet efficacy in healthy human volunteers.

Results: The formulation developed was found to be highly palatable and able to produce an anti-sweet effect for a duration of 30 min. Any sweet foods consumed within this duration of time failed to taste sweet.

Conclusions: The formulation developed may serve as a simple, novel and workable remedy for people to control their sweet cravings, which in turn could help in controlling caloric intake derived from sweet substances and thus help in the control of diabetes and obesity.

1. Introduction

Taste is consistently reported as a major influence on food consumption. However, this includes not only taste *per se*, but also smell, appearance and texture of food. These sensory aspects are thought to influence food choice in particular. A liking for sweetness and a dislike for bitterness are considered as innate human traits present from birth. It is the basic biology that dictates a liking for sweetness across lifespan. Hence there is an increase in food intake as palatability increases of which sweetness is a contributing factor (Sorensen et al., 2003; Adam et al., 2012). Sweet foods have an undeniable sensory appeal. Food is not only solely regarded as a source of nourishment but often consumed for the pleasure value it imparts. If the food is not sweet, its consumption will be undeniably reduced as it does not provide the pleasure or satisfaction (Clarke, 1998; Nasser, 2001).

Gymnema sylvestre is a well-known herb for its anti-sweet and antidiabetic properties in both traditional and Ayurvedic medicine. After chewing a few leaves of the plant, one is unable to detect a sweet taste and sugar crystals are reported to feel like sand that slowly dissolve in the mouth. The unusual property of this plant was first mentioned in the literature in 1847. The gymnemic acids present in *G. sylvestre* have the similar molecular configuration of glucose; hence they temporarily occupy and block the sugar receptors on the tongue. Attributable to the neutralization of the receptors, the sugary foods won't taste sweet and cannot be relished, thereby giving the instant ability to curb sugar cravings (Edgeworth, 1847).

Traditional methods of preparation for the administration of herbal medicines such as *G. sylvestre* may result in poor palatability, reduced compliance and efficacy. Thus to maximize their efficacy there is a need for more palatable, patient friendly dosage forms of some herbal medicines to be developed. Earlier, herbal medicines were not considered for development as novel formulations due to processing difficulties and the lack of scientific justification for the use of purified extracts. However, modern phyto-pharmaceutical research has started to address the scientific needs (such as determination of pharmacokinetics, mechanism of action, site of action, accurate dose required) of herbal medicines to guide the development of novel formulations and routes of administration (Goldman, 2001; Kusum et al., 2010).

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http://dx.doi.org/10.1016/j.hermed.2015.09.005
2210-8033/

The anti-sweet properties of *G. sylvestre* have been extensively tested in humans by several research groups, but most of the investigations employed *G. sylvestre* leaves, which are slightly bitter (Gordon and Ava, 1981; Gent et al., 1999; Kazuko and Shlgenobu, 1991; Kurihara, 1969; Meiselman and Halpern, 1970a,b; Paul and Richard, 1983). None of these groups however have developed a dosage form of this herb. *G. sylvestre* is also available as extracts standardized to the quantity of gymnemic acid present which could be incorporated via a modern method of drug delivery into a patient friendly formulation such as a tablet or capsule to provide a dietary aid for persons having difficulty controlling their sweet substance intake. As life style changes play a very important role in controlling obesity and diabetes, the anti-sweet dosage forms could help in reducing weight by diet control. As a preventative measure an anti-sweet formulation could delay the onset of obesity and diabetes.

In the present study, the aim was to prepare an anti-sweet formulation of *G. sylvestre* extract in the form of a mouth dispersing tablet for the local delivery of gymnemic acid in the oral cavity. *G. sylvestre* has a slight bitter and unpleasant taste, making it highly unpalatable in its natural form; it was decided therefore to mask the bitter taste of the herb by developing a more patient friendly tablet that quickly dispersed providing fast and immediate action in addition to improving its palatability. It was proposed to clinically evaluate the prepared formulation in healthy human volunteers in two phases. In the first phase the palatability of the tablet that had been taste masked was determined in terms of masking the bitterness, palatability in the mouth and *in vivo* disintegration time. In the second phase volunteers were first trained for sweetness evaluation and then the anti-sweet potential of the developed formulation was determined in qualified subjects.

During the development of an anti-sweet dosage form of G. *sylvestre* two issues needed to be addressed. First, was to make the drug release quickly in the mouth which was achieved by preparing the tablets to be immediately dispersible on administration. Fast dispersible tablets are solid unit dosage forms which contain medicinal substances that disintegrate or dissolve rapidly within a few seconds or minutes. Out of the various technologies available (Pfister and Ghosh, 2005; Yourong et al., 2004) for making fast dispersible tablets, the direct compression with superdisintegrants was selected for the *G. sylvestre* extract. This method is based on the fast disintegration action established by superdisintegrants such as croscarmellose sodium, crospovidone and sodium starch glycolate. They improve disintegration efficiency and are used at low levels in solid dosage forms, typically 1–15% of mass relative to the total mass of the dosage unit (Kuccherkar et al., 2003; Rudnic et al., 1980).

The second issue was the bitter taste of the herb which was masked by a three part de-bittering system. Masking agents cover up unwanted flavours without altering the active materials. The three part de-bittering or masking system was composed of (1) physiological competition, (2) sweetness profiling and (3) flavor creation. (1) The physiological competition can reduce the overall perception of bitterness by competing with the receptors for the bitter receptors neuron firings. Sodium citrate, an acid salt, can be added to cause competition within the receptors. As the receptors will respond to the salt, it can reduce the response to the bitter stimuli and cause an overall reduction of the bitter taste. Sodium chloride can also compete within the channel receptors with the bitter stimuli to reduce the overall perception of bitterness. Menthol which can have a cooling effect in the mouth can also distract the organoleptic effects of the bitter taste. (2) There are a variety of high-intensity sweeteners that can be used either alone or in combination with each other to provide a specific sweetness profile. An extended sweetness profile can be developed for *G. sylvestre* by using a combination of sugary sweeteners (to create an initial sweetness burst which would then be blocked by the effect of drug) and non-sugary sweeteners (for extended sweetness). (3) A range of different complimentary flavour types such as mint, raspberry, lime, citrus or coffee could be used to enhance the de-bittering by distracting the organoleptic effects. Menthol could also have been added to create both flavor and a cooling effect in the mouth. By combining the physiology of the taste receptor actions with the art of flavor creation and sweetener addition, the extremely bitter taste of the *G. sylvestre* can be successfully masked to make the formulation more palatable.

From the authors search of the literature the dose of *G. sylvestre* 75% extract was calculated as 10 mg per dose to be effective in its anti-sweet action in the mouth (Meiselman and Halpern 1970b; Warren, 1969). The objective of the present work was to develop a taste masked, fast, dispersible tablet and then evaluate it *in vivo* for efficacy. The herbal formulation thus developed may be useful as a dietary aid in controlling caloric intake derived from 'sweets'. Thus, it can help in controlling obesity and subsequently also diabetes.

2. Materials and methods

The dry extract of *G. sylvestre* was obtained from Sami Labs, Bangalore. The extract was standardized to contain 75% gymnemic acids. The following tablet excipients were used: Microcrystalline cellulose (Avicel PH 101), Crospovidone (Kollidon CL), Cross-linked sodium carmellose (acdi-Sol), Sodium starch glycolate type A (Primojel), Colloidal silicon dioxide (Aerosil;), Mannitoal (Mannogem), Citric Acid, Sucralose, Sodium Chloride, Talc, and Magnesium stearate.

Table 1
Composition of different batches of directly compressed tablets of *Gymnema sylvestre* extract.

Ingredients	O1	O2	O3	O4	O5	O6	O7	O8	O9
G. sylvestre extract	2%	2%	2%	2%	2%	2%	2%	2%	2%
Mannogem	25%	25%	25%	25%	25%	25%	25%	25%	25%
MCC	61%	59%	57%	61%	59%	57%	61%	59%	57%
Citric acid	5%	5%	5%	5%	5%	5%	5%	5%	5%
Sucralose	3%	3%	3%	3%	3%	3%	3%	3%	3%
Sodium chloride	1%	1%	1%	1%	1%	1%	1%	1%	1%
Crospovidone	2%	4%	6%	–	–	–	–	–	–
Sodium starch glycolate	–	–	–	2%	4%	6%	–	–	–
Croscarmelose sodium	–	–	–	–	–	–	2%	4%	6%
Colloidal SiO_2	1%	1%	1%	1%	1%	1%	1%	1%	1%
Menthol	1%	1%	1%	1%	1%	1%	1%	1%	1%
Talc	0.5%	0.5%	0.5%	0.5%	0.5%	0.5%	0.5%	0.5%	0.5%
Flavour	QS	QS	QS	QS	QS	QS	QS	QS	QS

QS: quantity sufficient.