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Understanding health-related properties of bushmint (*Hyptis*) by pharmacokinetic modelling of intestinal absorption

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ABSTRACT

Hyptis species including *H. pectinata* and *H. verticillata* are widely used in ethnopharmacology, wherein plant-extracts are ingested to treat a range of ailments including gastro-intestinal afflictions. However, the intestinal pharmacokinetics of these extracts are poorly understood. Recently, a Phytochemical Absorption Prediction (PCAP) model was reported, allowing prediction of the time for ingested phytochemicals to reach maximal plasma concentration (T_{max}) in humans via intestinal absorption. The aim of this study was to explore the pharmacokinetics using the PCAP model and the potential mechanisms of medicinal efficacy of the phytochemicals within the *Hyptis* species. The composition and medicinal efficacy of *Hyptis* phytochemical extracts were collated from published literature. Physicochemical properties of phytochemicals including molecular mass and lipophilicity were calculated to allow the prediction of the associated T_{max} in humans using the PCAP model. The identification of known antimicrobial compounds indicated potential efficacy via mediation of pathogenic load. Application of the PCAP model identified that traditional ethnomedicinal uses of *Hyptis* extracts result in likely regulation of postprandial oxidative stress based on T_{max} of phytochemicals. The medicinal efficacy of *Hyptis* extracts may occur via antimicrobial activities and regulation of oxidative stress by phytochemicals. These results highlight the usefulness of the PCAP model by informing ingestion pharmacokinetics of phytochemicals.

1. Introduction

The bushmints (members of the *Hyptis* genus) have generated substantial interest due to their widespread usage within ethnopharmacology as infusions and concoctions, to treat a broad range of ailments including throat inflammation, fungal infections and pain relief (Aquino et al., 2011; De Sousa, 2011; Raymundo et al., 2011). Whilst the exact modes of action are yet to be confirmed, analyses of *Hyptis* oil extracts have identified several functional components with antibacterial and antifungal activities such as monoterpenes which account for almost 96% of the extractable oils (Malan et al., 1988). The medicinal efficacy of *Hyptis* oils is therefore thought to be associated with the abundances and bio-accessibilities of active phytochemical constituents (Picking et al., 2013). These phytochemicals are treated by the body as xenobiotics and are consequently only transiently present in the body post-ingestion (Holst and Williamson, 2008). The capacity for these phytochemicals to impart medicinal benefit may therefore be limited if the timing of absorption is not aligned with the timing of stressors that the medicinal compounds act to mediate. Accordingly, medicinal efficacy may be influenced by the pharmacokinetics of the phytochemicals, such as the time delay to achieve peak concentration in plasma after ingestion (T_{max}). It is hypothesised that the alignment of T_{max} with the timing of stressor onset, referred to as 'bio-matching', is required for optimal treatment efficiency by herbal phytochemicals (Selby-Pham et al., 2017a). Investigations of phytochemical uptake post ingestion commonly utilise *in vitro* cell culture models such as Caco-2 cells. Whilst these types of cell models have become well established for the prediction of phytochemical bioavailability, inferences regarding associated phytochemical pharmacokinetics may be unreliable (Selby-Pham et al., 2017c). To complement *in vitro* methods, an *in silico* phytochemical absorption prediction (PCAP) statistical model was recently developed to calculate T_{max} of phytochemicals post human ingestion (Selby-Pham et al., 2017b). The PCAP model has been applied to characterise absorption pharmacokinetic windows or 'functional fingerprints' of phytochemicals from functional foods (Selby-Pham et al., 2017a), which may provide valuable insight to the uptake times and opportunity for health benefits by herbal medicinal compounds. This article aims to utilise these recently developed approaches to predict the pharmacokinetics of medicinal phytochemicals within the ethnomedicinal bushmint species *Hyptis pectinata* (mint weed) and *Hyptis*

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verticillata (consumption weed).

2. Materials and methods

The mint weed essential oil phytochemical profile was produced with relative abundances as an average of gas chromatography-mass spectrometry (GC–MS) results presented in Tchoumbougnang et al. (2005) (which used a HP1 fused column coupled to a Helett-Packard apparatus), Koba et al. (2007) (which used a DB5 column coupled to a Helett-Packard apparatus), Nascimento et al. (2008) (which used a DB5 column coupled to a Shimadzu apparatus), Serafini et al. (2012) (which used a DB5 column coupled to a Shimadzu apparatus), and Feitosa-Alcantara et al. (2017) (which used a RTx-5 column coupled to a Shimadzu apparatus). The phytochemical profile of extracts from consumption weed root was sourced from the review by Picking et al. (2013). Physicochemical properties of phytochemicals, including molecular mass and lipophilicity descriptor log P were calculated using the Molinspiration online property calculation toolkit (http://www.molinspiration.com). The PCAP model was used to calculate T_{max} of phytochemicals present in the mint weed and consumption weed extracts following oral ingestion in human, as described in Selby-Pham et al. (2017b). The 'functional fingerprint' of phytochemical extracts, describing the predicted T_{max} profiles of the extracts, was produced as described in Selby-Pham et al. (2017a).

3. Results

The physicochemical properties (log P and molecular mass) of phytochemicals in consumption weed root extract were used to predict their T_{max} post human ingestion using the PCAP model (Table 1, Supplementary Table S1). This was performed for oral intakes in the forms of either liquid, semi-solid, or solid. The consumption weed root extract phytochemicals had molecular masses ranging from 314.43 to 484.63 and were relatively hydrophobic with log P ranging from 3.86 to 4.99. When ingested in liquid form, the predicted T_{max} of consumption weed phytochemicals ranged from 1.57 to 2.40 h. When ingested in semi-solid form (e.g. pastes), the predicted T_{max} of consumption weed phytochemicals ranged from 0.79 to 1.12 h. When ingested in solid form, the predicted T_{max} of consumption weed phytochemicals ranged from 1.77 to 2.16 h.

Relative abundances of the mint weed essential oil phytochemicals were plotted versus their associated T_{max} to obtain their predicted T_{max} profile 'functional fingerprints', for absorption in humans (Supplementary Table S2). This was performed for the three intake forms of liquid (Fig. 1a), semi-solid (Fig. 1b) and solid (Fig. 1c). When ingested in liquid form, the T_{max} of mint weed phytochemicals ranged from 0.76–1.92 h with predominant peaks occurring at 1.19, 1.29 and 1.58 h (Fig. 1a). When ingested in semi-solid form, the T_{max} of mint weed phytochemicals ranged from 0.56 to 1.67 h with predominant peaks occurring at 0.78, 0.85 and 1.20 h (Fig. 1b). When ingested in solid form, the T_{max} of mint weed phytochemicals ranged from 1.59 to 2.65 h with predominant peaks occurring at 1.76, 1.85 and 2.25 h (Fig. 1c). In all three intake forms, these predominant peaks were associated with calamusenone, caryophyllene oxide and β-caryophyllene respectively which combined accounted for 49% of the relative abundances.

4. Discussion

The bushmints (genus *Hyptis*) are commonly used in ethnopharmacology to treat a range of ailments (Supplementary Table S3). Herein, we focused on the phytochemical profiling of *H. verticillata* (consumption weed) and *H. pectinata* (mint weed) as examples of medicinal bushmints, both of which are utilized in the treatment of gastrointestinal problems and pains (Asprey and Thornton, 1955; Picking et al., 2013). Whilst the specific modes of action of these plant-based medicines are yet to be definitively identified, the efficacy is expected to be based on the chemical nature and relative abundances of phytochemical constituents (Edeoga et al., 2005).

The medicinal efficacy of bushmint traditional medicines may relate the antimicrobial activity of the plant-extracts against common pathogens such as *Staphylococcus aureus*, one of the most prevalent foodborne disease worldwide and leading cause of gastroenteritis (Lima et al., 2013). *H. verticillata* extracts have shown antimicrobial activity (including against *S. aureus*), potentially associated with the hypothesised antimicrobial activity of 7-acetyl-12-methoxyhorminone (Picking et al., 2013) or the verified anti-*S. aureus* activity of the royleanones (Rijo et al., 2014). Similarly, *H. pectinata* extracts have shown broad-spectrum antimicrobial activity against gram-positive bacteria including *S. aureus* (Pereda-Miranda, 1995). The functional fingerprinting results indicated that calamusenone, caryophyllene oxide and β-caryophyllene were the main contributors to the 3 major peaks in *H. pectinata* profiles (Fig. 1), which, when combined, accounted for 49% of the relative abundances of phytochemicals. Calamusenone has not been extensively studied, so whilst insecticidal activity has been demonstrated (Yanzhang et al., 2010), the antimicrobial activity of this compound is suspected but is yet to be definitively verified (Santos et al., 2008). The antimicrobial activities of caryophyllene oxide and β-caryophyllene have been tested, and whilst selective against only a subset of bacteria, both showed antibacterial activities against *S. aureus* (Dahham et al., 2015; Ulubelen et al., 1994). Accordingly, medicinal efficacy of bushmint infusions or concoctions utilized in ethnopharmacology may result from the ingestion of antimicrobial compounds extracted from the plant materials.

Additionally, the medicinal efficacy of bushmint traditional medicines may relate to the capacity of extracted phytochemicals to mediate oxidative stress. For example, postprandial stress and its associated gastrointestinal disorder are caused by the oxidative stress response occurring during the consumption and digestion of a meal (Sies et al., 2005), with postprandial insulinemia (Huang et al., 2016) and lipemia

Table 1
Calculated values of T_{max} for main phytochemicals in roots from *Hyptis verticillata* (consumption weed), associated with oral intake in liquid, semi-solid or solid forms.

Phytochemical	Log P[a]	Molecular mass[a]	Predicted T_{max}[b] (h)		
			Liquid	Semi-Solid	Solid
7-acetyl-12-methoxyhorminone	4.56	388.50	1.98	0.97	1.98
7-acetoxy-16-benzoxy-12-hydroxyabieta-8,12-diene-11,14-dione	4.55	484.63	2.40	0.96	1.98
11,14 dihydroxy-12-methoxyabieta-8,11,13-triene-7-one	4.99	346.47	2.01	1.12	2.16
11,14-dihydroxy-12-methoxy–18(4-3βH) abeo-abieta-4(19),8,11, 13-tetraene-7-one	3.86	350.50	1.57	0.79	1.77
7-acetoxy-12-methoxyabieta-8,12-diene-11,14-dione	4.54	392.54	1.99	0.96	1.98
Royleanone	4.68	316.44	1.76	1.00	2.03
7,6-dehydroroyleanone	4.53	314.43	1.70	0.96	1.97

[a] Calculated using Molinspiration software (http://www.molinspiration.com/).
[b] Calculated using the phytochemical absorption prediction (PCAP) model (Selby-Pham et al., 2017b).