Is there a potential of misuse for Magnolia officinalis compounds/metabolites?

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Abstract

Magnolia officinalis-based herbal preparations are used for the treatment of a range of different health problems. Magnolia bark contains magnolol, metabolized to tetrahydromagnolol (THM), and honokiol, all presenting with both cannabimimetic and GABA-ergic activities, hence of possible attraction to vulnerable individuals/recreational misusers. Hence, we aimed here at: reviewing the literature relating to Magnolia misusing issues; describing, through an assessment of related anecdotal online reports, the magnolia possible misusing potential; obtaining an overview of Magnolia products’ online acquisition possibilities.

No peer-reviewed papers relating to Magnolia abuse/misuse/dependence/addiction were identified. Conversely, from a range of websites commenting on Magnolia misuse issues it emerged that there may be three groups of Magnolia misusers: a) subjects with a psychiatric history already treated with benzodiazepines, being attracted to Magnolia bark as a ‘natural sedative’; b) subjects with a polydrug misuse history, ingesting Magnolia with a range of other herbs/plants, attracted by the compound GABA-ergic/cannabimimetic activities; c) subjects naive to the misusing drugs’ scenario, perceiving Magnolia as a natural dietary supplement or as a weight control compound.

To the best of our knowledge this is the first paper commenting on the possible Magnolia derivatives’ potential of misuse. Magnolia’s recent increase in popularity, mainly as a sedative, may be arguably due to its peculiar pharmacological properties; acceptable affordability levels; virtually worldwide favourable legal status; and customers’ attraction to a product being perceived as ‘natural’ and hence somehow ‘safe’. Future, potent, synthetic magnolol and honokiol structural analogues could however contribute to increasing the number of synthetic GABA-ergic/cannabimimetic misusing compounds.

Key words
Drug misuse; novel psychoactive substances; magnolol; honokiol; THM; GABA receptors; cannabinoid receptors; anxiety; herbal highs; synthetic cannabinoids; synthetic cannabimimetics; Spice
Introduction
Magnolia officinalis is part of the Magnoliaceae family; its bark contains magnolol and honokiol (Lee et al., 2012; Watanabe et al., 2002), respectively identified in ratios of approximately 4:1 (Kotani et al., 2005; Tsai and Chen, 1992), together with α-/β-/γ-eudesmol and methyleugenol (Wrigley, 2009). Magnolia bark-containing preparations (Houpo or Koboku; for a thorough review of the issue, see Lee et al., 2011; and Wrigley 2009) have a role in both Chinese and Japanese traditional herbal medicine (Rempel et al., 2012; Xu et al., 2008), reportedly possessing a range of activities, including: anti-oxidant; anti-inflammatory/antibacterial; antithrombotic/anti-platelet; hypoglycaemic; smooth muscle relaxant (Squires et al, 1999; Sohn et al, 2007); weight control (Garrison and Chambliss, 2006); anti-dyspeptic/prokinetic (Oikawa et al., 2005); antiepileptic (Chiou et al., 1997); and hepato-protective (Lee et al., 2012).

The mechanisms underlying Magnolia compounds’ central pharmacological activities are not clear (Lee et al, 2011). Magnolol is a partial agonist at both endocannabinoid receptor subtypes (CB1 and CB2); with a higher potency at CB2 (Ki 1.44 ± 0.10 μM) as opposed to CB1 (Ki 3.15 ± 1.65 μM; Rempel et al, 2012). THM, the main faecal magnolol metabolite, is still active both as a full CB1 agonist and as a CB2 partial agonist (e.g. CB1 Ki 2.26 ± 0.89 μM; CB2 Ki 0.416 ± 0.089 μM) (Rempel et al, 2012). Furthermore, honokiol shows full agonist properties at CB1 receptors, whilst acting as antagonist/inverse agonist at the CB2 receptor subtype. Hence, magnolol, honokiol and THM show higher intrinsic activity at CB1 than tetrahydrocannabinol/THC, the main cannabis euphoriant compound (Fattore, 2016). Magnolia compounds’ interaction with gamma-aminobutyric acid-A/GABA-A and muscarinic receptors (Squires et al, 1999; Lin et al, 2007) may be consistent with reducing anxiety levels observed in small-scale clinical studies (Kalman et al., 2008; Mantani et al., 2002). Indeed, in animal behavioural models honokiol and dihydrohonokiol are described as producing anxiolytic, diazepam-like, effects (Alexeev et al, 2012; Kuribara et al, 1998).

Conversely, the magnolol/honokiol antidepressant-like activities observed in preclinical models may be associated with alterations in serotonin turnover in the frontal cortex, striatum and nucleus accumbens (Nakazawa et al, 2003). Magnolol and honokiol seem to have similar pharmacokinetic characteristics, with half-lives being both almost dose-independent and of first-order (Lee et al, 2011). Both compounds can readily pass the blood brain barrier (Tsai et al., 1996; Wang et al, 2011); magnolol oral bioavailability is in the region of 10% (Wrigley, 2009) and is extensively metabolized in the liver, with glucuronides being its major metabolites. Similarly, glicuronidation and sulphation are the main metabolic pathways for honokiol (Bohmdorfer et al, 2011; Hattori et al, 1986).

Magnolia derivatives’ could interact with other sedatives, increasing the risk of drowsiness/motor reflex depression (Wrigley 2009). Although high-dosage magnolol may induce in vitro hepatotoxicity (Kao et al, 2010), acute/long term preclinical/clinical toxicity studies have not identified any biological alterations associated with Magnolia-based (including mints/gums) preparations’ intake (Liu et al., 2007; Wrigley, 2009). However, tremors; peri-labial numbness; sexual and thyroid dysfunction; fatigue; and headache have been anecdotally reported by small numbers of Magnolia users (Kalman et al 2008).

Magnolia GABA-ergic and cannabimimetic activities could arguably be of attraction to vulnerable individuals/recreational misusers. Hence, we aimed here at: reviewing the literature relating to Magnolia compounds’ misusing issues;
assessing the Magnolia bark/derivatives’ possible misuse potential whilst considering the related anecdotal online reports; and providing an overview of the Magnolia online acquisition possibilities from both English- and Italian-language websites.

Materials and methods
To identify the peer-reviewed papers commenting on Magnolia misuse issues, a comprehensive search on the Embase, Scopus; Google Scholar and Pubmed/Medline databases was performed using the following key words: (Magnolia) AND (abuse OR misuse OR poisoning OR dependence OR addiction). No language or time restrictions were placed on the electronic search; focus was on clinical data only and covered the period up to August 9th, 2016.

To identify information on Magnolia misusers’ first-hand experiences, a qualitative/observational approach on selected websites was carried out. In doing so, between January 2014 and March 2016 a range of qualitative Google searches were carried out, both in English and in Italian, using key words such as ‘Magnolia and abuse’, ‘Magnolia and misuse’, and ‘Magnolia and experience’. The first 2 pages/20 hits per keyword (e.g. 60 per language; e.g. 120 links) were considered. A number of websites were excluded, since: not relevant (e.g. referring to Magnolia role in gardening); being duplicates; or requiring a registration/payment procedure. Conversely, a range of fora posts/threads relating to a few Magnolia themes, including: psychoactive effects; dosage/intake modalities; tolerance/withdrawal; untoward effects; and use in combination with other psychoactive compounds; were specifically analysed. No posts/other contributions to fora discussions were made, and no information or clarification of content was sought by the researchers.

To obtain an overview of Magnolia products’ online purchase possibilities, a range of Google searches in English and Italian were carried out, using the ‘Magnolia bark to buy’; and ‘Magnolia bark purchase’ key words. The information provided by the identified links on: safety; consumer reviews; and purchasing costs were analyzed.

To assess possible increase over time in terms of interest in Magnolia-related issues, a range of Google Trends (Google Trends, 2016) searches were here carried out. Starting from 2004, this approach shows how often a particular search-term is entered across the various regions of the world/variou
languages. The search term queries included: ‘Magnolia’; ‘Magnolia bark’; ‘Magnolia bark + cannabis’; ‘Magnolia bark + cannabimimetic’; ‘Honokiol’; ‘Magnolol’; ‘Magnolia + purchase’; ‘Magnolia bark + tranquilizer’; ‘Magnolia bark + antidepressant’; ‘Magnolia bark + euphoria’; and ‘Magnolia bark + misuse’. Ethics’ approval for the study was granted by the University of Hertfordshire School of Pharmacy Ethics Committee, on December 15th, 2010 (reference code PHAEC/10-42), with a further 5-year extension of the approval having been granted in November 2013.

Results
No peer-reviewed papers relating to Magnolia abuse/misuse/dependence/addiction were here identified. Conversely, some 41 websites relating to Magnolia issues were here assessed, with most (e.g. 21) being dedicated to its purchase/acquisition. A further 13 websites included specific/illustrative comments on the Magnolia compounds’ associated psychoactive effects. Analysis of the 137 relating posts identified from here showed that in most (e.g. n=133) cases users were commenting on the
Magnolia-related anxiolytic/sedative effects, whilst n=4 posts emphasized its cannabimimetic/recreational effects. Further reasons to self-administer with Magnolia included achievement of antidepressant; analgesic; anti-nausea; and weight control effects (see Table 1). Specifically, three groups of Magnolia misusers were here tentatively identified: a) subjects with a psychiatric history, self-administering with Magnolia as a sleeping aid; as a ‘natural alternative’ to prescribing sedatives; or to cope with benzodiazepines’ withdrawal; b) subjects with a polydrug misuse history, allegedly ingesting Magnolia to: enhance/modulate the effects of cannabimimetic/‘Spice’ drugs and/or of other GABA-ergic molecules, especially phenibut and gammahydroxybutyrate-GHB. A range of herbs/plants, including Mytragina speciosa/’Kratom’, and Sceletium tortuosum/’Kanna’; were here reportedly co-administered with Magnolia (see Table 1); c) subjects naive to the misusing drugs’ scenario, perceiving Magnolia either as a natural dietary supplement or as an affordable way to lose weight. Misuse of magnolia bark compounds mostly seemed to occur orally, with smoking and vaporizing intake techniques being also reported, at dosages in the range of 60-900 mg. Adverse, transient, untoward effects included: mouth/throat numbness; lightheadedness/tiredness; and dizziness. Although specific withdrawal symptoms were not described, levels of tolerance were anecdotally reported (see Table 1). A vast range of Magnolia vending websites, especially when searching in English, was identified. Branded with various commercial names, Magnolia derivatives were offered either as pure concentrates/extracts or mixed with other substances. Overall, these commercial websites labelled their products as ‘safe’, ‘legal’, and ‘pure’, whilst describing themselves as ‘verified merchants’, offering a ‘100% satisfaction guaranteed/top choice supplement’ deal. Purchase prices were in the range of euros 5-55 /USD 6-60 per 60 Magnolia bark extract tablets, with variations depending on the quantity of items purchased. ‘Google Trends’ search queries with the term ‘Magnolia’ have been associated with levels of interest since April 2015, especially from: Poland, the US, and the Philippines. Conversely, the ‘Magnolia Bark’ searches peaked in 2004 and 2013, whilst the ‘Magnolia purchase’ related searches have remained stable since 2004. The ‘Magnolia bark + tranquilizer’; ‘Magnolia bark + antidepressant’; and ‘Magnolia bark + misuse’ searches have been associated with levels of interest both in 2012-3 and since February 2016, mostly from the US regions. Finally, only minimal levels of interest were here observed when the search term ‘Magnolia bark’ was associated with ‘cannabis’; cannabimimetic’; and ‘euphoria’.
Table 1: Misuse of magnolia bark extract; online users’ accounts and illustrative examples of English and Italian vending websites

<table>
<thead>
<tr>
<th>Sought effects</th>
<th>Illustrative experiences</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reduction of anxiety levels</td>
<td>• Magnolia bark extract ... has all the anti-anxiety effects of a benzo, minus the impairment in motor skills ... (Drugs-forum.com)</td>
</tr>
<tr>
<td></td>
<td>• Magnolia bark extract works well for relaxation purposes. I would try the Magnolia Bark Extract on its own before adding it to Ambien (e.g. zolpidem) + Kratom, because the effect could be strongly synergistic ... (Drugs-forum.com)</td>
</tr>
<tr>
<td></td>
<td>• Magnolia bark extract has all the anti-anxiety effects of a benzo, minus the impairment in motor skills ... (Amazon.com)</td>
</tr>
<tr>
<td>Sleeping aid</td>
<td>• Magnolia bark extract ... helps the mood also ... (Amazon.com)</td>
</tr>
<tr>
<td></td>
<td>• Magnolia bark extract ... has all the anti-anxiety effects of a benzo, minus the impairment in motor skills ... (Drugs-forum.com)</td>
</tr>
<tr>
<td></td>
<td>• Magnolia bark extract ... helps the mood also ... (Amazon.com)</td>
</tr>
<tr>
<td>Mild antidepressant-effect</td>
<td>• Magnolia bark extract ... has all the anti-anxiety effects of a benzo, minus the impairment in motor skills ... (Drugs-forum.com)</td>
</tr>
<tr>
<td></td>
<td>• Magnolia bark extract ... has all the anti-anxiety effects of a benzo, minus the impairment in motor skills ... (Drugs-forum.com)</td>
</tr>
<tr>
<td>To ‘chill out’; alone or in association with alcohol</td>
<td>• Magnolia bark extract ... has all the anti-anxiety effects of a benzo, minus the impairment in motor skills ... (Drugs-forum.com)</td>
</tr>
<tr>
<td></td>
<td>• Magnolia bark extract ... has all the anti-anxiety effects of a benzo, minus the impairment in motor skills ... (Drugs-forum.com)</td>
</tr>
<tr>
<td>To use as a safer alternative of phenibut</td>
<td>• Magnolia bark extract ... has all the anti-anxiety effects of a benzo, minus the impairment in motor skills ... (Drugs-forum.com)</td>
</tr>
<tr>
<td></td>
<td>• Magnolia bark extract ... has all the anti-anxiety effects of a benzo, minus the impairment in motor skills ... (Drugs-forum.com)</td>
</tr>
<tr>
<td>To control appetite/weight</td>
<td>• Magnolia bark extract ... has all the anti-anxiety effects of a benzo, minus the impairment in motor skills ... (Drugs-forum.com)</td>
</tr>
<tr>
<td></td>
<td>• Magnolia bark extract ... has all the anti-anxiety effects of a benzo, minus the impairment in motor skills ... (Drugs-forum.com)</td>
</tr>
<tr>
<td>To relieve nausea</td>
<td>• Magnolia bark extract ... has all the anti-anxiety effects of a benzo, minus the impairment in motor skills ... (Drugs-forum.com)</td>
</tr>
<tr>
<td></td>
<td>• Magnolia bark extract ... has all the anti-anxiety effects of a benzo, minus the impairment in motor skills ... (Drugs-forum.com)</td>
</tr>
<tr>
<td>Intense relief of headaches</td>
<td>• Magnolia bark extract ... has all the anti-anxiety effects of a benzo, minus the impairment in motor skills ... (Drugs-forum.com)</td>
</tr>
<tr>
<td></td>
<td>• Magnolia bark extract ... has all the anti-anxiety effects of a benzo, minus the impairment in motor skills ... (Drugs-forum.com)</td>
</tr>
<tr>
<td>2-4 capsules Magnolia bark ... can double the effects of phenibut (true, I have tried this with others and they agree). They quoted 2 to 5 times potentiation I think. My brother said he noticed a 75% increase, for me it is a doubling effect ...</td>
<td></td>
</tr>
<tr>
<td>Prescribing medicines/recreational drugs/herbs and plants reportedly taken in combination with Magnolia-related compounds</td>
<td></td>
</tr>
<tr>
<td>Use in concomitance with:</td>
<td>• GABAergics: phenibut; zolpidem; THC-like molecules; THC, synthetic cannabimimetics; Cognitive enhancers; Herbs/plants: Mytragyna speciosa/Kratom; Erythrina mulungu/Mulu ngu; Bacopa; Sceletium tortuosum/Kanna; Rhodiola rosea; and Ashwagandha</td>
</tr>
<tr>
<td></td>
<td>• Magnolia Bark Extract works well for relaxation purposes. I would try the Magnolia Bark Extract on its own before adding it to Ambien (e.g. zolpidem) + Kratom, because the effect could be strongly synergistic ... (Drugs-forum.com)</td>
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</tr>
</tbody>
</table>

Experience reports

I purchased this product to use as a supplement to phenibut, as you cannot use phenibut often without risks. I have suffered from insomnia for many years and have used quite a few prescription medications...all have given me a morning hang over effect...For several months now, I have been taking one Magnolia bark capsule to help me fall back to sleep, and I am very pleased with the results... (Amazon.com)

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Discussion and Note as a sedative/sleeping aid, but polydrug derivatives’ putative potential of misuse

To the best of our knowledge were seen rudely as a sedative/sleeping aid, but polydrug derivatives’ putative potential of misuse. The compound may be misused mainly as a sedative/sleeping aid, but polydrug intake patterns were here identified as

Intake modalities; dosages; and side effects

Ingestion routes; dosages advised

- ‘…i take about 600mg to 800mg at a time, any less doesn’t do much.’ (Amazon.com)
- ‘…not to be taken sublingually…’ (Amazon.com)
- ‘….i use it with Coconut Milk (source of fat for enhanced absorption) and its pretty tasty as long as only using a small amount….. I have tried using Magnolia Bark Extract sublingually at approximately 200mg…. it killed the taste buds on the front half of my tongue. I could no longer taste even pure salt. It tasted like beach sand.’ (Drugs-forum.com)

Withdrawal; tolerance; side effects

- ‘….magnolia i find to be good and not causing any extra anxiety or withdrawal problems…’ (Longecity.org)
- ‘….One thing I did notice about magnolia bark extract i is if you take it two days in a row , the second day isn’t as good as the first day…’ (Drugs-forum.com)
- ‘….The only problem with the extract, for me at least, is that it starts to loss some of its magic with frequent use, so I just use it one or twice a week ‘…. (Amazon.com)
- ‘I have recently tried Lift Mode Magnolia bark powder - put in hot water and drank. It caused entire mouth and throat to go numb; then next day became extremely sore as though burnt…. ’ (Webmd.com)
- ‘…..I was taking 200mg for 8 days and developed vertigo one morning. After about a week the vertigo seems to have stopped, but I still have a mild ringing in the ears and feel light headed at times…..’ (Herbwisdom.com)

Illustrative examples of English/Italian language websites allegedly offering Magnolia bark extract for purchase

English language
http://www.ebay.co.uk/
AllStarHealth.com
http://www.matricargo.com/
www.amazon.com
http://www.amazon.co.uk
http://www.puritan.com
http://www.vitacost.com
www.healthmonthly.co.uk
http://www.swansonvitamins.com/
http://www.walgreens.com/
http://vitaminsbecause.biz/
http://www.zoya.bg/
http://vitaminstore.biz/
http://ww.nutricargo.com/
http://hawaii-pharm.com/
etc

Italian language
http://www.biovea.com/
http://www.supersmart.com/
http://www.ebay.it/
http://it.made-in-china.com/
http://www.fedelfarma.com/
www.vitaminty.com

Note: SWIM: somebody who is not me. Spelling mistakes have not been edited, but rude words have been deleted. Most data collected from online forums that could be seen as personal identifiable (e.g. usernames, complete URLs for specific threads etc) were here anonymized. The online users’ accounts here reported were selected on the basis of being considered particularly illustrative of the clinical issue anecdotaly described.

Discussion and Conclusions

To the best of our knowledge this constitutes the first description of the Magnolia derivatives’ putative potential of misuse. The compound may be misused mainly as a sedative/sleeping aid, but polydrug intake patterns were here identified as
well. Furthermore, synthetic magnolol and honokiol structural analogues could contribute to increasing the number of synthetic cannabimimetic/GABA-ergic misusing compounds.

The web plays a huge role in the modification of both psychotropics’ availability and changes in drug scenarios (Schifano et al, 2015; 2016), and one could argue that the vast levels of Magnolia online acquisition possibilities may reflect the large number of potential customers. Indeed, the recent increase of Magnolia popularity, mainly a sedative, here identified may arguably be due to its peculiar pharmacological properties; acceptable affordability levels; virtually worldwide favourable legal status; and customers’ attraction to a product being perceived as ‘natural’ and hence somehow ‘safe’.

The pharmacological effects of magnolol, THM, honokiol, and 4-O-methylhonokiol might be used as a new generation of anti-abstinence, anti-craving and neuroprotective drugs, with their GABA-ergic activity possibly being useful as well for the treatment of convulsions, spasms, and associated pain (Coppola and Mondola, 2014). Conversely, in considering magnolol/THM cannabimimetic properties, recent work has shown that it is possible to design and synthesize a series of (TH)magnolol analogues with extremely high CB1 receptor affinity, selectivity, efficacy, and potency (Fuchs et al, 2013). Indeed, this is the case of the dual CB1/CB2 full agonist 2-(2-methoxy-5-propyl-phenyl)-4-hexylphenol (Ki CB1: 0.00957 µM; Ki CB2: 0.0238 µM; Fuchs et al, 2013). To put things into perspective, THC displays a modest affinity (Ki: 35-80 nmol) at the CB1 receptor, whilst AM-694, the highest affinity molecule within the synthetic cannabimimetic group (SC; ‘Spice’; ‘K2’) displays a Ki: 0.1 nmol (Fattore, 2016). Indeed, SC (Schifano et al 2015; 2016) intake has been associated with a number of psychopathological/psychiatric manifestations (e.g. ‘spiceophrenia’; Papanti et al, 2014). Apart from their CB1-agonist activities, further honokiol/magnolol analogues present with very potent GABA-A receptor allosteric modulators (Fuchs et al, 2014), hence defining a new GABA-ergic/cannabimimetic psychotropics’ class.

There are a number of possible limitations of the present study; a multi-lingual analysis of a larger sample of websites could have provided better levels of information. Furthermore, only publicly available web sites/fora were monitored here, and further data of interest could possibly have been identified by the analysis of the ‘deep web’/‘dark net’ material (Orsolini et al, 2015). We made no Magnolia purchase attempts, hence one could argue about the product content/dosage being delivered. Overall, anecdotal reports are only partially reliable and it may be inappropriate to trust information obtained from the internet without independent verification. Since no peer reviewed papers relating to Magnolia misuse issues were identified, the present conclusions mainly relied on sources (e.g. web sites) characterized by levels of unreliability. Hence, a bias may well have been introduced here, and the manuscript’s conclusions should be considered as Authors’ opinions. Only large scale, adequately controlled, clinical studies can give a clear indication of a drug characteristics and adverse effects. However, in line with present observations, previous studies from our group (Schifano et al, 2009; Siemann et al, 2006) have clearly suggested that the increase in online trafficking/debate about a specific psychoactive drug typically precedes the occurrence of clinical incidents at the population level.

The issue of Magnolia products’ misuse may be a reason for concern; consumers may not be made fully aware of the pharmacological activity, and possible medical consequences, of the compound(s) they are ingesting. Furthermore, Magnolia products’ misuse may often occur in the context of polydrug intake, and
the pharmacodynamics/pharmacokinetics’ interactions of magnolol/THM/honokiol with other substances are not known.

As with any centrally active drug, physicians should carefully evaluate patients for history of drug abuse and observe them for signs any products’, including Magnolia bark, misuse.

Acknowledgments
This paper was supported in part by grants of the European Commission (Drug Prevention and Information Programme 2014-16; contract no. JUST/2013/DPIP/AG/4823; EU-MADNESS project). Further financial support was provided by the EU Commission-targeted call on cross border law enforcement cooperation in the field of drug trafficking - DG Justice/DG Migrations and Home Affairs (JUST/2013/ISEC/DRUGS/AG/6429) Project EPS/NPS (Enhancing Police Skills concerning Novel Psychoactive Substances; NPS).

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Squires RF, Ai J, Witt MR. Honokiol and magnolol increase the number of [3H] muscimol binding sites three-fold in rat forebrain membranes in vitro using a filtration assay, by allosterically increasing the affinities of low-affinity sites. Neurochem Res 1999; 24: 1593-602.


