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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

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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 ± 00.89 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/various 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'.

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Table 1: Misuse of magnolia bark extract; online users' accounts and illustrative examples of English and Italian vending websites

	Sought effects
Reduction of anxiety levels	'... magnolia bark extract ... has all the anti-anxiety effects of a benzo, minus the impairment in motor skills ...' (Drugs-forum.com) '….Non-sedating, non-euphoria anxiety relief. Best alternative I've found to asking a doctor for a pill for your anxiety….' (Amazon.com)
Sleeping aid	'... herbal alternatives to benzos for sleep?...' (herbwisdom.com) '……apparently it is very similar to a light benzo dose....' (Bluelight.org) '…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)
Mild antidepressant-effect	'... magnolia bark extract ... it helps the mood also ...' (Amazon.com)
To 'chill out'; alone or in association with alcohol	'... couple scoops of magnolia bark extract after work are perfect for chilling for the rest of the evening ...' (Amazon.com) '…real good with a few beers, especially at the end of a long day …'
To use as a safer alternative of phenibut	'...I had heard great things about phenibut for social anxiety, but not-so-great things about withdrawal/dependance, and I needed something mild enough that I could take it at work or driving without looking or feeling 'on something'. So I settled on this magnolia bark extract, and like many of the other reviewers find it effective ...' (Amazon.com) '….I purchased this product to use as a supplement to phenibut, as you can not use phenibut often without risks …. phenibut can be a little too strong sometimes……Magnolia bark fits those needs for me…..' (Amazon.com)
To taper off/to lighten the withdrawal effects of benzodiazepines, phenibut, tobacco, alcohol, GBL, opiates	'... honokiol ... very useful for benzo addicts trying to taper ...' (Bluelight.org)
To control appetite/weight	'... magnolia bark extract ... seem to work for appetite control quite well. Days when I took Magnolia Bark, I'd often forget to eat. It wasn't that I couldn't eat or genuinely didn't want to. It was that it just didn't really occur to me. When it would occur to me, I'd go "yeah, I guess I am kind of hungry" and grab something. But I wouldn't overeat, even though I hadn't eaten in twelve hours ...' (herbwisdom.com)) '…I tried Magnolia Bark Extract to help relieve stress and to stop the cortisol from creating belly fat…' (herbwisdom.com)
To relieve nausea	'... magnolia bark extract ... excellent product great for relieving nausea too! ...' (Amazon.com)
To use as a relief from headaches	'... honokiol ... is often helping me out with tension headaches especially ...' (entheogen-network.com)
	Prescribing medicines/recreational drugs/herbs and plants reportedly taken in combination with Magnolia-related compounds
Use in concomitance with: • *GABAergics:* phenibut; zolpidem; • *THC-like molecules:* THC; synthetic cannabimimetics; • *Cognitive enhancers* • *Herbs/plants:* Mytragina speciosa/kratom; Erythrina mulungu/Mulungu; Bacopa; Sceletium tortuosum/Kanna; Rhodiola rosea; and Ashwaghanda	'... 2-4 capsules Magnolia bark ... can double the effects of phenibut (truly, 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...' (forum.mindandmuscle.net) '….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) '….It felt kind of like a muscle relaxer when I smoked cannabis….I took about 10mg and placed it over a bowl of cannabis (Michiganmedicalmarijuana.org) '... SWIM would imagine that with Spice Tropical Synergy the honokiol and magnolol in the magnolia bark synergises with the effects of the JWH-018 too ...' (Drugs-forum.com) '…..I found it to be an especially good adjunct for using with cognitive enhancers, like hydergine or lucidril, as it seemed to balance out their stimulating properties….' (Amazon.com) '….ashwaghanda and magnolia i find to be good and not causing any extra anxiety or withdrawal problems. ….Anyway I recently ordered some magnolia bark along with some 98% honokiol extract and I'm gonna mix the two….. Also ordered Mulungu which Ive heard good things about, possibly Kanna though I'm a bit weary of kanna since it might have ssri action and I seem to be sensitive to that. I agree with who ever said mixing some bacopa and rhodiola together, as I've had some good results mixing this with the magnolia and ashwaghanda. ….' (Longecity.org) '…..is very effective for reducing Kratom's nausea….' (Drugs-forum.com)
	Experience reports

	'… 8:30pm - Swim put the 50mg of isolate in a glass of water and drank. 9:02pm - Swim noticed a little something in the back of his mind which can only be described as a flash of complete tiredness/pure disreguard for my surroundings (this could have been placebo effect, not sure it was very short in duration, maybe 10-20secs) 9:17pm - What was once a flash is now steady. Swim says he feels relaxed and at the same time he feels a disreguard for his surrounding or anything that may have been troubling him in the day. 9:37pm - Peak was reached, Swim said he still feels relaxed but the feeling of disreguard has subsided slightly. 9:45pm - Swim decided to does with another 50mg of isolate. 10:22pm - Swim once again slightly feels disreguard for surroundings. 10:53pm - Swim feels like some of his everyday problems seem to not matter as much. Things just seem trivial that might normal bother swim. Swims tiredness has increased. Swim feels that the possibility for anxiety are pretty much slim to none no matter what my have come his way. Swim also notices a very slight feeling of warmth that can be associated with warm opiate blankets, however; in this case it just feels more relaxing instead of euphoric (again it is subtle, but its there). 11:20pm - Swim still feels effects and is still tired. Swim says he must go to bed. Summary: Although swim doesn't suffer from anxiety the occasional day does presents itself. Swim will deffinately keep this in his toolbelt for future use against anxiety. Swim also feels that in just 50mg dosages this could deffinately be used as tool to relax at the end of the day before bed to take the edge off. Swim just wonders if plain bark powder could be utilized in the same way and in what dosages of powder would be taken …' (Entheogen-network.com)
	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 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.nutricargo.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://www.super-smart.eu/ http://www.iherb.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.vitaminity.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 anecdotally 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 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 (*K*i CB1: 0.00957 μM; *K*i CB2: 0.0238 μM; Fuchs et al, 2013). To put things into perspective, THC displays a modest affinity (*K*i: 35-80 nmol) at the CB1 receptor, whilst AM-694, the highest affinity molecule within the synthetic cannabimimetic group (SC; 'Spice'; 'K2') displays a *K*i: 0.1 nmol (Fattore, 2016). Indeed, SC (Schifano et al 2015; 2016) intake has been associated with a number of psychopathological/psychotic 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.

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