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The contractile capabilities of various herbal constituents on uterine smooth muscle and their shared constituent presence involved with anti-inflammatory/antioxidant mechanisms

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Abstract
Labor induction and augmentation can be affected by the use or consumption of unique medicinal plants that produce smooth muscle contractions in uterine tissues. An awareness of the commonalities of the specific herbal constituents among uterotonics is valuable information. This review of the primary literature reports the use of 21 plants and has shown that the phytochemical constituents such as prostaglandins, oxytocin, and triterpenoid saponins are involved in producing positive contractile responses. Other constituents such as diosgenin (a steroid saponin), ferulic acid, tannic acid, phenolic and flavonoid compounds have been reported to promote relaxation or demonstrate no response. These same plants were also documented to have anti-inflammatory and antioxidant properties, and employ mechanism which involve some of these same biological constituents. As a result of this review, investigations on ten unique plants, previously not reported to modulate uterine contractile behaviors, are recommended in an effort to determine their uterotonic potential. This is based on their documentation as presenting anti-inflammatory and antioxidant behaviors, as well as having prostaglandins, oxytocin, and/or triterpenoid saponins constituents. These results may aid in the selection of additional unique plant species which may be of use in promoting labor.

Keywords: medicinal plants, herbal constituents, uterotonics, anti-inflammatory/antioxidants

Introduction

Throughout history, natural remedies have been a common resource for treating disease and promoting general health. The use of medicinal plants in alternative medicine is still practiced in traditional cultures around the world, and one such use is for the induction and/or augmentation of labor.

Labor induction focuses on mechanisms that result in the contraction of uterine smooth muscle that will favor a safe and eventual delivery of the fetus. Natural remedies, such as aromatherapy, topical applications of essential oils, and consumption of a variety of extracts have been recommended and are administered by midwives as well as health care providers in many traditional settings [1 - 4]. The quest to better understand the mechanisms employed by the active phytochemical constituents of these medicinal plants, which result in uterine contractile responses, is worthy of attention.

A review of the literature illuminates that some uterotonics also possess the ability to reduce inflammation and/or demonstrate antioxidant behaviors. This stages the inquiry to determine whether such medicinal plants, whether used for promoting labor or reducing inflammation, share some of the same biological constituents. The purpose of this literature review was to provide a greater support and understanding of this hypothesized correlation.

Objectives of the review

This review is presented as a "synthesis-of-two-fields" review [5] in an attempt to provide new insights about one field of study (medicinal plants that are uterotonic) by bringing in literature from another area (medicinal plants that have anti-inflammatory/antioxidant behaviors). The plan of action to achieve this goal included the objectives that follow.

1. To survey several traditionally used medicinal plants that have been documented to contract isolated uterine smooth muscle tissues.
2. To summarize the documented (proposed and/or determined) biologically active constituents which are common in their ability to modulate uterine contractility.
3. To determine if these same medicinal plants have also been reported to demonstrate anti-inflammatory and/or antioxidant behaviors.

4. To further survey additional medicinal plants that, thus far, have only been documented for their anti-inflammatory and/or antioxidant properties, and recommend that they be investigated for their potential to induce/augment labor based on their biologically active constituents.

Materials and Methods

The information on the common constituents of medicinal plants involved with uterine smooth muscle contractions and anti-inflammatory/antioxidant behaviors was gathered from databases including PubMed, Google Scholar, Science Direct, and EBSCO. The articles that were selected had publishing dates between 1887-2021. Key words that were used in the search included (in alphabetical order): anti-inflammatory, antioxidant, composition, contractions, constituents, genus-species, midwifery, *in vitro*, labor, smooth muscle, and uterus.

Results and Discussion

Medicinal plants reported to contract isolated uterine smooth muscle tissues

Table 1 presents 21 medicinal plants (Column I: Genus-species, Column II: common and/or other names) that were selected from the literature based on their published ability to positively contract isolated mammalian uterine tissues harvested from mice, rats, or rabbits. It was deduced (when possible) from the manuscripts cited (Column III) that plant extracts were administered as aqueous preparations into an organ bath. Therefore, it is likely that some of the biologically active constituent(s) responsible for the contractile behaviors were hydrophilic.

The phytochemical constituents considered to be biologically active, and that have been identified and/or isolated from these plants, are listed in Column IV. Evidence that these same medicinal plants (which contract uterine tissue) also have anti-inflammatory and/or antioxidant behaviors is listed in Column V.

Table 1: Medicinal plants that are documented to both contract the uterus and exhibit anti-inflammatory/antioxidant activity

Colum I Genus species	Column II Names	Column III Positive contractile responses (plant organ, if noted)	Column IV Common constituents (alphabetical)	Column V Anti-inflammatory/antioxidant activity
Astragalus genus	huáng qí milkvetch	Ding *et al.* 2013 [6] Shahrani *et al.* 2020 [7]	alkaloids, flavonoids, polyphenolic compounds, saponins [7, 8]	Bratkov *et al.* 2016 [8] Shahrani *et al.* 2020 [7]
Actaea racemosa	black cohosh	Hatchfeld 2010 (roots) [9] Neuenschwander (roots) 2018 [10]	alkaloids, ferulic acid, saponins, tannins [11]	Ruhlen *et al.* 2008 [12] Yang *et al.* 2009 [13]
Anethum graveolens	dill	Chumber and DeGolier 2020 (seeds) [14]	alkaloids, anthocyanin, flavonoids phenolics, glycosides, monoterpenoids, oxytocin, saponins, tannins [15 - 19]	Zhu *et al.* 2015 [18] Oshaghi *et al.* 2015 [19] Tuntipopipat *et al.* 2009 [20]
Angelica spp.	female ginseng garden angelica wild angelica	Shi *et al.* 1995 [21] Puk and DeGolier 2021 (seeds) [22]	ferulic acid, N-butylidenephthalide, lingustilide, Z- saponins [23, 24]	Sarker and Nader 2004 [25] Chao and Lin 2011 [23] Han and Guo 2012 [26] Orhan *et al.* 2016 [27] Kim *et al.* 2018 [28]
Carica papaya	papaya	Chumber and DeGolier 2020 (fruit) [14] Hser 2020 (fruit, leaf, seeds) [29]	alkaloids, anthraquinones, flavonoids, glycosides, saponins, tannins [30]	Pandey *et al.* 2016 [31] Sagnia *et al.* 2014 [32]
Carthamus tinctorius	safflower	Delshad *et al.* 2018 (fruit, leaves, flowers, seeds, oil) [33]	arachidonic acid, linoleic acid, saponins [34]	Zhou *et al.* 2014 [35]
Caulophyllum thalictroides	blue cohosh	Berger and DeGolier 2008 (roots/rhizomes) [36]	alkaloids, triterpene saponins [37 – 40]	Lee *et al.* 2012 [41]
Codonopsis pilosula	dang shen poor man's ginseng	He *et al.* 2015 (roots) [44]	alkaloids, phenylpropanoids saponins [43, 44, 45]	Tsai *et al.* 2013 [46] He *et al.* 2015 [42]
Costus speciosus	wild ginger	Lijuan *et al.* 2011 (rhizomes) [47]	arachidonic acid, diosgenin, linoleic acid [47]	Vassilopoulos *et al.* 1997 [48] Bayles and Usatine 2009 [49]
Crescentia cujete	calabash	Theis *et al.* 2017 (fruit) [50]	linoleic acid, saponins [51, 52]	Ejelonu *et al.* 2011 [52]
Cuminum cyminum	cumin	Chumber and DeGolier 2020 (seeds) [14]	alkaloids, anthraquinone, courmarin, flavonoids, glycosides, proteins, saponins, steroids, tannins [53]	Al-Snafi 2016 [54]
Leonurus cardiaca	motherwort	Neuenschwander 2018 [10]	alkaloid (leonurine), flavonoids, mono-, di-, tri -terpenes, N-containing compounds, phenylpropanoids, sterols, tannins, volatile oils [55, 56]	Wojtyniak *et al.* 2013 [56]
Leonurus aretemisiae	Chinese motherwort	Kong and Ng 1974 [57]	diterpenoids [58]	Khan *et al.* 2012 [58]
Mitchella repens	Partridge berry	Neuenschwander 2018 [10] Horner and DeGolier 2021 [59]	alkaloids, saponins, tannins [60 - 65]	Bergeron *et al.* 1996 [66] Sparg *et al.* 2004 [67]
Oenothera biennis	evening primrose	DeGolier *et al.* 2017 (seeds) [68]	arachidonic acid, linoleic acid, saponins [34]	Khanapure *et al.* 2007 [69] Calder 2013 [70]
Ricinus communis	castor seed	Tunaru *et al.* 2012 (seed oil) [71] Quam *et al.* 2016 (seeds) [72]	alkaloids, flavonoids, glycosides, saponins, steroids [73, 74]	Vieira *et al.* 2000 [75] Oloyede 2012 [76] Maia *et al.* 2017 [77]
Rubus idaeus	red raspberry	Zheng *et al.* 2010 (leaves) [78] Olson and DeGolier 2016	Saponins [80]	Patel *et al.* 2004 [80] Noratto *et al.* 2016 [81]

		(leaves) [79]		
Salvia sclarea	clary sage	DeGolier and Adamson 2021 (seeds) [82]	linoleic acid, saponins [83, 84]	Kostić *et al.* 2017 [85] Tsai *et al.* 2018 [86]
Trachyspermum ammi	Ajwain *Carum copticum Ammi copticum*	Chumber and DeGolier 2020 (seeds) [14] Stephens 2019(seeds) [87]	saponins, thymol, *Trachyspermum ammi* protein [88]	Rajeshwari *et al.* 2011 [89] Yu *et al.* 2016 [90]
Trigonella foenumgraecum	fenugreek	Chumber and DeGolier 2000 (seeds) [14] McCutcheon 2020 (seeds) [91]	diosgenin, oxytocin, saponins [92 - 96]	Liu *et al.* 2012 [97] Akbari *et al.* 2019 [98]
Viburnum opulus	cramp bark	Neuenschwander 2018 (bark) [10]	saponins [99, 100]	Rychlińska 2008 [99] Polka *et al.* 2019 [100]

Common biologically active plant constituents affecting smooth muscle contractility as well as regulating and influencing anti-inflammatory/antioxidant responses

Seven of the common constituents found in this survey (see Table 1), along with their proposed mechanisms of action (if known) are described in more detail in the paragraphs that follow. Three of these constituents, or constituent groups, (linoleic acid, arachidonic acid, and prostaglandins, oxytocin, triterpenoid saponins) are reported in the literature to produce positive contractile responses in uterine tissues. Four other constituents, or constituent groups, (diosgenin, ferulic acid, tannic acid, phenolic and flavonoids) are reported to promote relaxation or produce no contractile response at all. This diversity in contractile responses may be attributed to both the molecular diversity of the constituents (as agonists) coupled with the variety of cell signaling pathways (receptors) on the uterus [3].

It is reasonable that the responses produced from individual constituents could well be attenuated, potentiated, synergistic, or simply masked when attention is given to whether the extract administered is representative of a plant-organ, the entire plant, or included in a formulary cocktail of a variety of plants.

Linoleic acid, arachidonic acid, and prostaglandins

Prostaglandins, as well as their precursors linoleic acid and arachidonic acid, have been detected in a large diversity of plant taxa [101]. Prostaglandins (PG) are derived from arachidonic acid, and linoleic acid is precursor to arachidonic acid [49]. Specific prostaglandins, such as PGE_2 or PGF_2 can contract uterine smooth muscle [102], and induce labor with dependence on Ca^{2+} influx through voltage-operated Ca^{2+} channels [103, 104].

While the synthesis of prostaglandin can function in the generation of the inflammatory response [105], it is suggested that under inflammatory conditions, the products derived from arachidonic acid metabolism can lead to lead to pro- or possibly, anti-resolving pathway activation [106].

Oxytocin

Oxytocin has been isolated from both fenugreek and dill species (see Table 1). In mammals, oxytocin signals calcium release from the sarcoplasmic reticulum [107, 108] and also is involved in signaling uterine intracellular pathways to produce prostaglandins [109]. Multiple anti-inflammatory behaviors under the influence of oxytocin (from neural input or infusions) have been recorded in animal models [110, 111].

Saponins

Saponins are glycosidic triterpenoids. Structurally, they are sugars attached to another organic molecule, such as a triterpenoid 30 carbon pre-curser skeleton molecule [112]. They have been confirmed in a number of plant species [113] and their distribution within fruits, flowers, leaves, stems, and roots and/or rhizomes is frequently found to be distinctive [114].

The amphipathic properties of saponins enable them to be cell permeating agents [115-118], causing invaginations and pore formation [34, 119, 120]. Within smooth muscle cells, this might provide the means for the influx of extracellular Ca^{2+} ions, successfully inducing smooth muscle contraction [121].

Saponins have also been demonstrated to exhibit potent anti-inflammatory behaviors [42, 112, 123, 124].

Diosgenin

Diosgenin is a steroid saponin derived from plants [125]. Although they are derived from the same carbon pre-curser skeleton molecule as triterpenoid saponins, they contain a distinctive 27 carbon characteristic when compared to the triterpenoid 30 carbon [126]. Variations within the substituent aglycone structures (triterpenoid or steroid) as well as the glycone (sugar) moieties account not only for their structural differences but also contribute to their diverse bioactivity [112]. For example, a study using rhizomes extracts from *Paris polyphylla* found rat uterine tissues to respond in either a positive or inhibitory contractile manner. This was proposed to be based on the variable structures of the steroidal saponins that were isolated from the extract [127] Furthermore, rhizome extracts from wild ginger, *Costus speciosus*, were shown to induce uterine smooth muscle contraction, but the isolated constituent diosgenin was observed to have either no effect or an inhibitory response [47]. This emphasizes the need for continued study to determine the biological actions observed from isolated constituents as opposed to the potential interactions with greater than one phytochemical.

The diosgenin constituent has also been shown to have a positive impact on both metabolic and inflammatory processes and antioxidant properties [128].

Ferulic acid

Ferulic acid is a component of lignin and is abundant in plant cell walls. Ferulic acid that is found bound to cell wall polysaccharides is absorbable [129]. Isolated ferulic acid was observed to decrease the spontaneous movements of the rat uterus *in situ* [130] and have an inhibitory effect on the contractility of mice uterine tissue *in vitro* [131].

Ferulic acid also reduces oxidation and inflammation. These compounds have also been shown to (1) reduce pro-inflammatory interleukin (IL)-6 or tumor necrosis factor (TNF)-alpha production, (2) enhance anti-inflammatory IL-10 production, or (3) reduce cyclooxygenase-2 or inducible nitric oxide synthase expression [132, 133].

Tannic acid

Tannins, common constituents of medicinal plant crude extracts, have been shown to antagonize contractions evoked by a variety of agonists in isolated rat uterus, likely by affecting calcium availability for contraction [134]. Tannic acid has also been shown to reduce smooth muscle contractility in vascular tissue [135].

Tannic acid, as an effective scavenger of reactive oxygen species, is a well-known antioxidant [136] and has also been shown to reduce neutrophil recruitment and pro-inflammatory cytokines, all markers of reducing inflammation [137].

Phenolic and flavonoid constituents

Plant flavonoids are both secondary metabolites [8, 138] and polyphenols [139]. The flavanol quercetin suppressed isolated uterine horns from adult rats that were pre-contracted with $PGF_{2\alpha}$, oxytocin, and carbachol [140]. Other isolated flavonoids, such genistein and kaempferol, relaxed KCI-induced contractions in rat uterine smooth muscle by increasing levels of intracellular cAMP [141]. Extracted flavonoids from *Leonurus japonicus* have also been found to inhibit isolated rat uterine tissues [142].

Phenolic and flavonoid constituents are also influential in producing antioxidant activity and demonstrating anti-inflammatory behaviors [139, 143-148].

Further studies for determining potential medicinal plants that may demonstrate uterotonic properties.

It became apparent during this review that when searching the available literature on medicinal plants, many more publications were found on plant anti-inflammatory and/or antioxidant behaviors as compared to the number of investigations reporting plant effectiveness as an uterotonic. For example, when using the search terms “plant antioxidant inflammatory behaviors”, a Google Scholar search (from 2017 to the present) reported 17,300 results. In contrast, when using the search terms “plant uterus smooth muscle contractions”, the search setting reported 3,690 results.

If the constituents of medicinal plants (1) that are known for their ability to inhibit inflammation and behave as an antioxidant, and (2) have any of the same biologically active constituents that are consistent with those also identified in other medicinal plants known for their uterotonic behaviors (see Table 1), and (3) they themselves have not been investigated for uterotonic behaviors, then investigating these plants might lead to additional discoveries of species that could be used to induce or augment labor.

Table 2 presents 11 medicinal plants (Column I: Genus-species, Column II: common and/or other names) that were selected from the literature based on their productive anti-inflammatory/antioxidant behaviors (Column III) and have been reported to contain phytochemical constituents (Column IV) known to contract uterine smooth muscle.

Table 2: Medicinal plants that are documented to be involved with anti-inflammatory/antioxidant behaviors *and* contain phytochemical constituents known to contract uterine smooth muscle

Column I Genus species	Column II Names	Column III Documentation of inflammatory/antioxidant activity	Column IV Reported constituents (documentation)
Bupleurum chinense	thorow- wax	Li *et al.* 2017 [149] Yuan *et al.* 2017 [124]	saponins [150, 151]
Codonopsis lanceolate	deodeok, lance asiabell	Xu *et al.* 2008 [153] Kim *et al.* 2010 [145] He *et al.* 2015 [42]	phenolics, flavonoids [145, 154, 155]
Dioscorea villosa	wild yam	Mehta 2018 [156] Alsawalha *et al.* 2019 [157]	arachidonic acid, diosgenin, flavonoids, linoleic acid, saponins, tannins [34, 156, 158]
Fallopia spp.	knotweed	Şöhretoğlu *et al.* 2018 [148] Lachowicz and Oszmiański. 2019 [159]	flavonols, phenolic acids, saponins [152, 159]
Gossypium herbaceum	cotton root, levant cotton	Kumar *et al.* 2011 [160] Reddy and Raju 2018 [161]	carbohydrates, flavonoids, glycosides, saponins, steroids, tannins [162, 163]
Ocimum basilicum	basil, great basil	Bilal *et al.* 2012 [164] Miraj and Kiani 2016 [165]	flavonoids, glycosides, saponins, steroids, tannins [166]
Ophiopogan japonicus	dwarf lilyturf	Hung *et al.* 2010 [144] Wang *et al.* 2017 [167]	flavonoid activity [167] steroidal saponins [168]
Salvia miltiorrhiza	red sage, Chinese sage, tan shen, danshen	Su *et al.* 2015 [169] Ma *et al.* 2016 [170]	flavonoids, phenolic acids, saponins, tanshinones [171]
Schisandrar chinensis	five-flavor berry, magnolia berry	Brüll *et al.* 2015 [172] Szopa *et al.* 2017 [173]	essential oils, flavonoids, lignans, phenolic acids, polysaccharides, triterpenoid saponins [174]
Smilax china	China root	Lee *et al.* 2017 [175] Shao *et al.* 2007 [176] Xie *et al.* 2018 [177]	chlorogenic acids, flavonoids, glycoside diosgenin, phenylpropanoid, phenolic acid, saponins, stilbene [128, 175, 176, 177]
Ziziphus jujuba	*jujube red date, Chinese date, Chinese jujube*	Huang *et al.* 2017 [146] Mesaik *et al.* 2018 [147]	Flavonoids, saponins [146, 147, 178, 179]

Conclusions

Several phytochemical constituents identified in medicinal plants have been shown to modulate smooth muscle contractile behaviors in uterine tissues. Results from this literature review highlighted that prostaglandins, oxytocin, and triterpenoid saponins can contract uterine tissues, while diosgenin (a steroidal saponin), ferulic acid, tannic acid, phenolic and flavonoid constituents result in an inhibitory response or produce no contractile response at all. These same reviewed plants were also documented to have anti-inflammatory and antioxidant properties, likely employing mechanisms involving some of these same biological constituents.

It is suggested then, that plants previously not been reported to modulate uterine contractile behaviors, be investigated for uterotonic potential based on their documentation as presenting anti-inflammatory and antioxidant behaviors, as well as having prostaglandins, oxytocin, and/or triterpenoid saponins constituents. Results from these investigations can then aid in the selection of additional unique plant species which may aid in the induction and/or augmentation of labor.

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