



## Potential Effects and Mechanisms of Action of Topical Wallflower (*Erysimum cheiri* (L.) Cranz) Administration in Anal Fissure

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### Abstract

Anal fissure is an ischemic ulcer that occurs in anoderm and it has no obvious etiology and pathophysiology in current medicine. Anal fissure has a profound history in Persian and Persian medicine and wallflower (*Erysimum cheiri* (L.) Crantz) has been a common medication in this case. Traditional oil and/or dilute decoction of wallflower has been introduced as an effective topical medicine for anal fissure in Persian medicine. The aim of this study was to demystify the ancient wisdom in administration of low-dose wallflower for anal fissure, via the view point of modern pharmacological mechanisms. The basic idea and source of information was according to Persian and Arabic medicine manuscripts of the medieval Islamic era. Electronic literature was searched for related phytochemical and pharmacological studies available in Scopus, Google scholar, Pubmed and ScienceDirect databases from 1900 to 2018. The results showed that different parts of wallflower contain several types of cardiotonic steroids, isothiocyanates and flavonoids. Low-dose topical cardiotonic steroids, below their  $IC_{50}$ , could have potential effects on the ischemic condition of anal fissure ulcer and collagen synthesis in the local fibroblasts, by stimulation of  $Na^+/K^+$  ATPase pump. Furthermore, other active compounds in wallflower are isothiocyanates that could be responsible for tissue protective effects by induction of Nrf2 expression and activating TRPA1 channels. Also wallflower flavonoids are responsible for anti-inflammatory, analgesic and wound healing properties. To the best of our knowledge, this is the first time that low-dose topical wallflower administration is hypothesized to have anal fissure healing potential in conventional medicine. This study has introduced a novel mechanistic approach for anal fissure treatment.

**Keywords:** Wallflower; *Erysimum cheiri*; fissure in Ano; Persian medicine

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### Introduction

Anal fissure is a painful ischemic ulcer which occurs in the anoderm [1]. Although a great deal of research has been directed on the etiology and pathophysiology of anal fissure, the current knowledge is still incomplete [2]. Common

assumption is that occurring acute anal fissure is due to a local trauma and pain which causes spasm of internal anal sphincter and the resulting hypertonia leads to local ischemia which yields interruption of wound healing in chronic anal

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fissure [3]. The exact etiology of is still uncertain, but spasm of the internal anal sphincter is a key point in the patient's features [2]. It is unclear whether the spasm has a pathogenic role in fissure formation or whether it is a response to the pain [4]. Furthermore, the process of shifting from acute fissure to non-healing chronic phase is not clear [3]. Anal fissure has a profound history and traditional physicians have documented strict observations on this complication. In Persian medicine (PM) manuscripts, anal fissure is called "Shiqaq" that means a crack in the anus, and several remedies are advised to have healing properties on this complication [5]. Avicenna the great Persian physician in 11<sup>th</sup> AD, has categorized the causes of anal fissure into five different major groups including anal dis-temperament, severe constipation, inflammation, hemorrhoids, and increased blood pressure in the terminal parts of the anal vessels. He has remarked general characteristics for remedies potentiated to treat anal fissure. He suggested that remedies should have the following characteristics: astringent, emollient, anti-inflammatory, and they should have a kind of wound healing properties [6]. Wallflower is emphasized in PM literature to have therapeutic effects on anal fissure, so this study has focused on its potential effects and probable mechanisms of action to treat anal fissure.

## Methods

The basic source of information of the study was according to PM and Arabic medical manuscripts such such as "al-Hawi fi al-tibb" [7], Canon of medicine [6], as well as a medicinal manuscript from Arabian scholar Ibn Nafis, i.e.: "Al-shamel fi-alsanaat-altebyah" [8], "Tohfah al-Mu'minin" [9], "Makhzan-aladviah" [10] and "Qarābādin-e-Salehi" [11]. On the other hand, electronic literature was searched to extract related pharmacological studies available in Scopus, Google scholar, Pubmed and ScienceDirect databases with terms of "anal fissure", "low-dose and cardiotoxic steroids", "topical and cardiotoxic steroids", "isothiocyanates and

wound healing", "flavonoid and wound healing" from 1900 until 2018.

## Results and Discussion

### Wallflower for anal fissure in traditional medicine

According to Persian and Arabic medical manuscripts in the medieval Islamic era perspective, flower, aerial parts and root of wallflower (figure 1) have been considered to be effective in anal fissure treatment when it is applied as a cerate formulation made of its dilute decoction or traditional oil [7-11].



**Figure 1.** Wallflower; Left: Flower heads and siliques (Photographed by Mr. Ghasemzadeh). Right: Painting from "Der Wiener Dioskurides: Codex medicus Graecus" manuscript (1<sup>st</sup> AD) [12]

Mechanisms for treatment of anal fissure in traditional medicine could be explained as increasing local blood circulation, reduction of local inflammation and acceleration of wound healing (table 1).

PM, which is the heritage of experimental studies on humans throughout history, has introduced a low-dose wallflower preparation [7]. It is necessary to emphasize that PM has administered dilute wallflower decoction which has low concentration with an appearance similar to that of water. PM believes that this dilute decoction possesses extreme beneficial effects to treat anal fissure, chronic wound and/or inflammations [7]. This study has attempted to explore the ancient wisdom behind this herbal formulation via the lens of modern pharmacological perspective. According to recent investigations, wallflower has three groups of active constituents that can play a role in anti-fissure properties (table 2).

**Table 1.** Traditional medicine mechanisms responsible for probable anal fissure curing of wallflower

Traditional medicine mechanism	Description	Result(s) on anal fissure	References
<i>Taltif</i> (attenuation)	Dilution of thick humors	Increase blood circulation	[8,9,11]
<i>Taftih</i> (deobstructing)	Opening obstructions	Increase blood circulation	[11]
<i>Tahlil</i> (dissolution)	Anti-inflammation	Reduce local inflammation	[8,9,11]
<i>Jali</i> (detergent)	Removing excess exudate	Accelerate wound healing	[8,9,11]

**Table 2.** Potential effects of wallflower active compounds on anal fissure according to allopathic medicine

Active constituents	Hypothesized mechanisms	Reference
Cardiotonic	Low-dose CTS stimulates Na <sup>+</sup> /K <sup>+</sup> ATPase pump which leads to protection against ischemia	[18]
steroids: - Strophanthidin - Cannogenol - Digitoxygenin - Bipindogenin - Uzarigenin	Promoting collagen synthesis in dermal fibroblasts by low-dose CTS could have wound healing properties.	[23]
Isothiocyanates:	Induction of Nrf2 and antioxidant defense in the ischemic ulcer of anal fissure	[21,24-26]
-Cheirolin -Ibirvirin	Transient receptor potential channels (TRP channels) and pain pathway	[27]
Flavonoids:	Selective Cox-2 inhibitory effects	[28]
- Isorahmnetin - Quercetin	Wound healing properties	[29]

### Wallflower for anal fissure in conventional medicine

Wallflower has several types of cardiotonic steroids (CTS) such as strophanthidin, cannogenol, digitoxygenin, bipindogenin, and uzarigenin groups [13-15]. The acceleration of wound repair by using topical cardiotonic steroids was experienced since the past era [16], but in recent years, a novel pathway is observed in vitro and in vivo, that shows low-dose CTS can stimulate Na<sup>+</sup>/K<sup>+</sup> ATPase pump and it could be responsible for wound healing properties and also protection against ischemic tissues [17,18].

Other active compounds of the herb are isothiocyanates (ITC), i.e. cheirolin and ibirvirin [14,19,20] that have shown critical protective roles in tissues and organs [21]. Also, wallflower flavonoids (isorahmnetin and quercetin derivatives) [19,22] can be responsible for anal fissure healing properties. To the best of our knowledge, there is no report of using wallflower in topical form for anal fissure in current medicine.

CTSs, ITCs and flavonoids are active chemical compounds in wallflower. According to previous studies, CTS has dose dependent effects on Na<sup>+</sup>/K<sup>+</sup> ATPase pump and in safe doses lower than IC<sub>50</sub> values, topical CTS has stimulatory effects on Na<sup>+</sup>/K<sup>+</sup> ATPase pump to recover ionic gradient, and also low CTS concentrations may promote collagen synthesis in fibroblasts. ITC induces Nrf2 and antioxidant defense and also TRPA1 could be the target site for ITCs in pain pathways. Furthermore, flavonoids are reported to be responsible for Inhibition of prostaglandin E2 (PGE2) in macrophages. Putting all together, it could be hypothesized that wallflower topical application can introduce a novel approach for

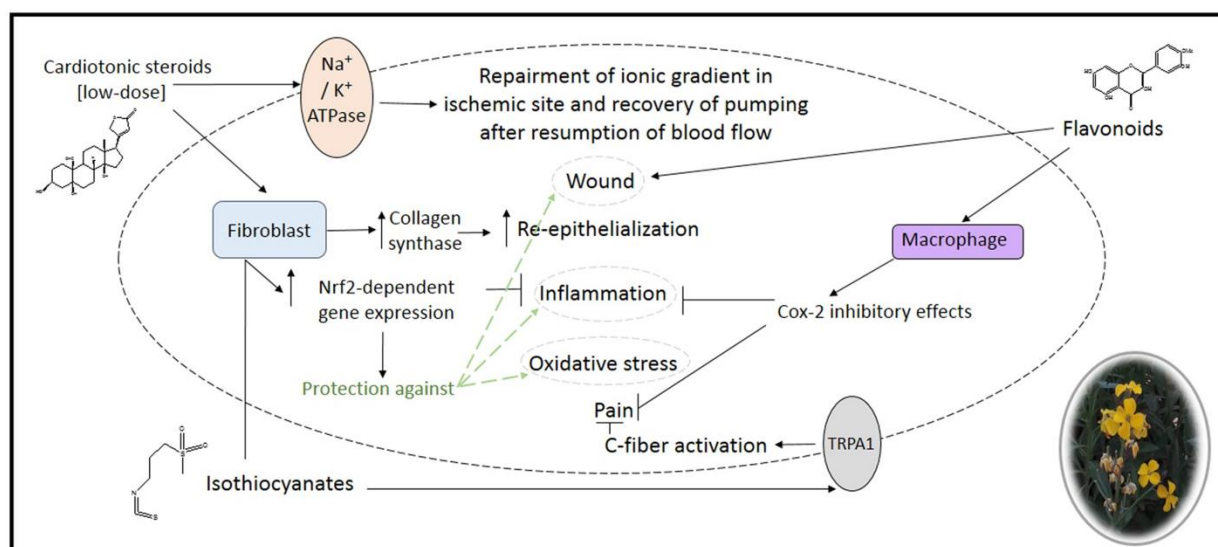
treating anal fissure. Five probable mechanisms related to anal fissure treatment have been discussed in this study (figure 2).

Nowadays, the effectiveness of active pharmaceutical ingredients is being studied with a focus on new concepts such as cell signaling. In this sense, efficacy is not just a path, and a series of events will be effective. System biology is also closely related to this issue. In addition to effectiveness, in this approach, many side effects can also be traced. This is important when it comes to traditional Iranian medicine for efficacy, with similar emphases on focusing on the overall effects of compounds. In the present study, we decided to investigate the different efficacy pathways in order to identify possible mechanisms of efficacy of traditional oil and/or dilute decoction of wallflower compounds in anal fissure.

### Stimulation of Na<sup>+</sup>/K<sup>+</sup> ATPase pump

Ischemia is a condition which disturbs ionic gradient among cell membrane. Oselkin et al. have shown that low-dose CTS (concentrations below IC<sub>50</sub>) on rat brain hippocampal slice cultures could have increasing effects on basal Na<sup>+</sup>/K<sup>+</sup> ATPase pumping which protects neurons from ischemia. Oselkin et al. have concluded that stimulation of Na<sup>+</sup>/K<sup>+</sup> ATPase pump could either inhibit the loss of ionic gradients or improve an accelerated recovery of pumping after resuming of blood flow [18].

This pharmacological study is a key point that may help us to demystify PM wisdom about administration of low-dose wallflower for the ischemic condition of anal fissure.



**Figure 2.** Potential effects and mechanisms of action of topical wallflower to treat anal fissure (T): Inhibition, reduction; (↑): Induction, stimulation

### Collagen synthesis in fibroblasts

There is large amount of information suggesting that transdermal application of digitalis glycosides (CTS drug) can promote and accelerate wound healing by collagen production in the human dermal fibroblasts [16,23]. There is a report revealing that human dermal fibroblasts exposed to CTS apparently increase the production of collagen. CTS showed accelerated wound healing properties in vitro or in vivo. As the result of Rajesh K. Naz study in 2008 show, CTS may eventually be a dermatological agent rather than cardiac medication [17]. Collagen is critical in wound healing process and it can decrease inflammation, stimulate re-epithelialization and promote the fibroblasts and keratinocytes growth in the ulcer site; consequently, collagen prevents loss of fluid from the ulcer and protects it from infections. In a clinical trial on childhood anal fissures, type I collagen has successfully healed all patients. In addition, the increased density of collagen fibrils as the consequence of topical CTS on ulcers may protect the skin from ischemic stress [4]. Long before oral administration of digitalis glycosides to treat heart diseases, their topical application for skin problems was common in middle ages [16]. Also, in India, an ointment containing digitalis glycosides has been marketed for wound healing [30]. Further development of CTS as therapeutic agents by topical application may be

of interest, especially in accelerating wound repairing [16,23]. So, it would be a safe and rational suggestion to evaluate the efficacy of low-dose CTS on anal fissure healing.

### Induction of Nrf2 and antioxidant defense

Nrf2-inducer ITCs (e.g.: cheirolin) may improve the antioxidant defense and stress response mechanisms in the cells [26]. According to many studies, Nrf2 plays a critical role in protecting tissues from a wide range of toxic conditions [21]. It is suggested that cheirolin and ibervirin can induce Nrf2-dependent gene expression in cultured fibroblasts, may improve antioxidant defense and stress response mechanisms in the cells [26], and cause protection against various severe complications such as chronic inflammatory diseases, neurodegenerative disorders and wounds [25]. Nrf2-mediated gene expression in keratinocytes may be responsible for wound healing [24]. Furthermore, according to a novel opinion for treatment of chronic anal fissure (CAF), as an ischemic ulcer, the process of healing is considered to be based on homeostatic mechanisms for balancing nitric oxide (NO) concentration and level of oxidative and nitroxidative stress in the ulcer [1]. Therefore, we hypothesized that the ischemic condition of anal fissure may be protected by Nrf2-inducing activity of cheirolin that results in antioxidant defense in this kind of stress condition.

### Transient receptor potential channels and pain pathway

Transient receptor potential channels (TRP channels) which exist in various animal cell types are mostly located on the plasma membrane and there are about 28 different types with similar structures [31]; for example, TRPA1 that is involved in some signaling pathways such as oxidative stress, nociception, and inflammation [32]. TRPA1 could be the target site for ITCs to activate the peripheral C-fibers [33]. It could be assumed that ITCs which are probes for TRP channels might have analgesic, antioxidant and anti-inflammatory properties. These therapeutic characteristics may have healing effects on the anal fissure.

### Inhibition of prostaglandin E2 (PGE2) in macrophages

It is reported that flavonoids are responsible for inhibitory effects on endogenous prostaglandin E2 (PGE2) in macrophage of RAW 264, as a selective COX-2 inhibitor. This pharmacological function may result in analgesic and anti-inflammatory effects [28]. Also, the wound healing properties of flavonoids have been reported [29].

Based on the above-described hypothesized mechanisms, it is expected that wallflower topical application (including CTS compounds, ITCs and flavonoids) can introduce a novel approach for anal fissure treatment.

### Conclusion

Anal fissure is a painful and common anal disorder. Its exact etiology and pathogenesis has not been fully understood in conventional medicine, but PM has described special mechanisms for anal fissure treatment according to the theory four humors. Topical administration of dilute decoction and/or traditional oil of wallflower has been considered to be effective for anal fissure treatment in PM. In modern phytochemistry, wallflower contains several types of cardiogenic steroids, isothiocyanates and flavonoids. Topical application of low-dose CTS (in concentrations lower than their  $IC_{50}$ ) can protect ischemic condition and stimulate collagen synthesis in anal fissure site. Furthermore, low-dose CTS should be safe for patients because the recommended concentration is much lower than toxic doses. The other active compounds in wallflower are ITCs that could stimulate NRf2-

expression in fibroblasts to have protective functions in stress conditions like ischemic ulcers (e.g. anal fissure). Also, ITCs may activate TRPA1 channels and C-fiber neurons to have pain relieving effects. The other active components of wallflower are flavonoids that could have anti-inflammatory, analgesic and wound healing properties. Bringing all together, we suggest topical application of low-dose wallflower as a potent medicinal preparation for anal fissure treatment. To the best of our knowledge, this is the first time that wallflower is hypothesized to have anal fissure healing potential.

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### Author contributions

Ghazaleh Mosleh, Abdolali Mohagheghzadeh and Amir Azadi conceived the presented idea. Ghazaleh Mosleh, Parnis Badr, Abdolali Mohagheghzadeh and Amir Azadi developed the theory. All authors discussed the results and contributed to the final manuscript.

### Declaration of interest

The authors declare that there is no conflict of interest. The authors alone are responsible for the content of the paper.

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#### **Abbreviations**

PM: Persian medicine; CTS: Cardiotonic steroids; ITC: Isothiocyanates; IC<sub>50</sub>: the half maximal inhibitory concentration; TRP channels: Transient receptor potential channels