Egypt. J. Chem. **Vol. 68**, No. 3. pp. 311 - 328 (2025)

Egyptian Journal of Chemistry

http://ejchem.journals.ekb.eg/

The Potential Of Genus Rumex As A Valuable Source Of Health-Promoting Metabolites: A Review Of Ethnomedicinal And Pharmacological Uses In The Treatment Of Skin Diseases

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Abstract

Skin diseases display essential disorders that threaten human health worldwide thus, there is an urge to find effective remedies for treating such diseases, especially from natural products which can be safer, more available, and cheaper than synthetic drugs. *Rumex* is one of the interesting drugs known to have a beneficial curing effect on various skin disorders especially through exerting antiaging and depigmentation activities. Genus *Rumex* is the second largest genus in the Polygonaceae family which consists of almost 200 species that are rich in various bioactive compounds such as flavonoids, anthraquinones, chromones, and stilbenes. The presence of numerous classes of bioactive constituents in Rumex was reflected in its pharmacological activities, thus the plant has potential anti-cancer, anti-diabetic, anti-inflammatory, and anti-oxidant effects together with its antiaging, anti-wrinkes and skin depigmentation. In this review, we provided an overview of the active compounds of Genus Rumex as well as its biological activity with a special emphasis on its effect on skin diseases.
Keywords: Rumex species; bioactive compounds; aging; skin disorders

1. Introduction

The skin is the largest body organ that is subjected to various external and internal stressors such as UV-radiations, toxins, immunodeficiency or autoimmune responses, oxidative stress, microbial attacks, and pathogens [1]. Such factors induce hyperpigmentation, chronic inflammation, aging, and skin diseases such as psoriasis, and eczema which may lead to skin cancer [2].

To offer effective protection for our skin, it is necessary to use sunscreens and antioxidants on a daily basis. Synthetic drugs have many limitations due to their side effects, low efficacy, and high cost, for this reason, plant-based alternatives are gaining strong attention especially since many natural products have proven effective as anti-inflammatory and antioxidants as well as antiaging agents both in preclinical and clinical trials [2, 3].

As the natural environment, local resources continue to play an important role in the investigation of more dietary and medical care for humans worldwide. The researchers today are more interested in investigating wild plants to be used as a solution for many health problems especially because of their low side effects and risk factors. Genus Rumex is distributed worldwide mostly in Europe, Asia, Africa, and North America comprising almost about 200 species, most of which have skin protecting effects, for example, *R. crispus* was reported to possess an antioxidant, inhibitory effect on metalloproteinases (MMP-1, MMP-8 and MMP-13) and high UV protective effect [4]. Rumex japonicas Houtt. in addition to its traditional use for skin diseases in Korea, it was reported to inhibit the phosphorylation of mitogen-activated protein kinase (MAPK) in atopic dermatitis –like skin lesions in mice [5]. Moreover, *Rumexaccidentalis* had shown a skin-lightening effect for melisma in a randomized, double-blind, placebo-control clinical trial [6].

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Received date 08 June 2024; revised date 31 July 2024; accepted date 13 August 2024
DOI: 10.21608/EJCHEM.2024.296162.9825

The focus of our review is to have an overview of the traditional uses and modern research that dealt with Genus *Rumex* with a special emphasis on its applications in treating various skin diseases. Also, we will show the various classes of chemical constituents that were identified in Rumex species using metabolomics techniques.

2. Traditional uses of the genus *Rumex*

Many members of the family Polygonaceae have reported anti-inflammatory, antiulcer, anti-asthmatic, and antidiarrheal activities. In addition to treating kidney diseases, psoriasis, eczema, and paralysis [3]. Among the genera belonging to the family Polygonacea, Genus *Rumex's* name originated from "rums" meaning to suck which refers to Roman's habit sucking leaves to allay thirst [7].
The leaves of various *Rumex* species were reported to have traditional uses, for example, the leaves of *R. acetosa, R. acetosella, R. abyssinicus, R. crispus, R. sanguineus, R. tuberosus*, and *R. vesicarius*were involved in making some food such as soups, salads, and sauces reflected its gastric effect [8]. Additionally, the roots of many *Rumex*species were reported to have a laxative effect. *R. acetosa* roots have been approved by the Korea Food and Drug Administration as one of the main food materials and also for its mild purgative effect as well as a remedy for the treatment of cutaneous diseases [8]. These valuable uses result in the increase in the cultivation of some *Rumex* species such as *R. acetosa* and *R. vesicarius* for their important medicinal effects [8].
Many *Rumex* species were also utilized in the traditional Chinese medicine for their therapeutic effect, such as *Rumexdentatus* which has been reported for the treatment of bacterial and fungal infections, the roots of *Rumexdentatus* as well was investigated for the treatment of acariasis, eczema, diarrhea, and constipation [9]. Also, *Rumexhastatus* is employed in the treatment of cough, headache, and fever. Moreover, in India and Pakistan, *Rumexcrispus* is used as a safe laxative and in the treatment of different skin problems such as ulcers and wounds [8]. A summary of the reported traditional uses is presented in **Table 1**.

Table 1 Summary of ethnopharmacological data about genus *Rumex*

Species	Pharmacological activity	Model	Results	Ref.
Rumexjaponicus Roots	Anti-colitis	*In-vivo* (DSS-induced mice)	It showed that methanolic extract of *Rumexjaponicus*reduce the Dextran- Sulfate Sodium-induced colitis by suppressing tight junction that occur in colonic tissues	[40]
Rumexnervosus Leaves	Anti-inflammatory	*In-vitro* (inflammatory cytokines *(IL-1β, IL-6, INF-δ, LiTAF.)* of chickens	The result showed that*Rumexnervosus* reduce inflammatory effect of these genes compared to standard Amprolium	[39]
R. acetosa L., Fruits,*R. acetosella L*Fruits,*R. confertusWilld* Fruits, R. crispus L. Fruits, R. hydrolapathumHuds. Fruits, R. obtusifolius L Fruits	Anti-microbial	Tested by agar and broth dilution method	The fruit ethanolic extract of *R. confertusWilld, R. crispus L., R. hydrolapathumHuds., R. obtusifolius L* have been showed anti-bacterial activityagainst *S. auerus and S. epidermidis.*	[48]
Rumexpatientia Roots	Anti-oxidant Cytotoxic agent	*In-vitro* (DPPH-scavenging assay)	flavan-3-ol-6-chlorocatechin and catechin compounds that are present on *Rumexpatientia*extracts showed highly activity against DPPH- radical scavenging assay	[47]

3. Medicinal properties of the genus *Rumex* against skin diseases

Nowadays, one of the most common diseases worldwide is the skin disorders. Skin aging is one of the most common regular disorders that both males and females suffer from, and they usually use cosmetic products as a solution or for its prevention as long as possible. Moreover, skin aging has many reasons and trigger factors such as genetic factors, environmental factors, UV radiation, metabolic processes, and hormonal changes [10]. In this aspect, *Rumex* species has been reported to possess potential anti-oxidant and anti-inflammatory effects that contribute greatly to control skin diseases [11]. *R. crispus*L. has been investigated for its biological activities against skin anti-aging and these are done by potentially inhibiting Matrix metalloproteinases (MMPs) (MMP-1, MMP-8, MMP-13) [4]. It also exerts antioxidant activities by DPPH, ABTS, NO, and phosphomolybdate methods and by measuring its Sun Protection Values (SPF values) [10]. Moreover, *R. japonica* has been investigated for its effect on atopic dermatitis and *in-vitro* and *in-vivo* anti-inflammatory effects [12]. Atopic dermatitis is one of the skin disorders that result from immunological abnormalities. It has several symptoms that may lead to chronic severe skin disorders [12]. Treatment of atopic dermatitis involves the use of steroids and antihistaminic drugs and thus long-term use may result in many side effects. Therefore, *R. japonica* has been investigated for its safety and efficacy treatment of atopic dermatitis [12]. A summary of the investigated medicinal activities of Genus *Rumex* against various skin diseases is presented in **Table 2**.

Table 2 : Medicinal activities of the genus *Rumex* against skin diseases

Species (plant part)	Extraction solvent	Pharmacological activity	Experimental model	Results	Ref.
Rumexcrispus (root, leaves and fruits)	-*n*-hexane extract -Dichloromethane extract -Ethylacetate extract -Ethanol -Ethanol: Water extract (70:30)	Anti-aging activity	*In-vitro* anti-oxidant (DPPH radical scavenging samples prepared at 25, 50,100, 200, 500 μg/mL, the absorbance measured at 520 nm using ascorbic acid as positive control DPPH Radical scavenging activity (%) = ((Abscontrol−Abssample)/Abscontrol))X 100 NO radical scavenging 25, 100, 200, 400, 800 μg/mL, the absorbance measured at 577 nm NO Radical scavenging activity (%) = ((Abscontrol−Abssample)/Abscontrol))X 100 ABTS radical scavenging 25, 100, 200, 400, 800 μg/mL, the absorbance measured at 734 nm using trolox as positive control ABTS Radical scavenging activity (%) = ((Abscontrol−Abssample)/Abscontrol))X 100	DPPH assay showed the highest significant result with ethanol and ethanol: water for all extracts. While ABTS radical scavenging showed the highest concentration (94%) in ethanolic root extract as well as NO radical scavenging showed (55.8%) in ethanolic and ethanol: water fruit extract	[10] **[49]**
			In-vitro (SPF measurements using Mansur equation) (100-200 μg/mL)	SPF value of on 100 & 200 μg/ml root extract showed lower value (6 & 13 SPF) compared to Leaf and fruit extract showed higher value (7 & 15 SPF)	

			*In-vitro*Matrixmetalloproteinases (MMP) enzyme inhibitor activity (MMP-1, MMP8, MMP-13) in six different concentration (50, 100, 200, 300,400 & 800µg/ml) compared with natural MMP-1, 8, 13 inhibitor NNG (90.8%, 93.8%, 91.9% at 1.3µg/ml) using inhibitor screening assay kit, the absorbance measured at 412nm in microplate reader	The result showed that highest inhibition appeared to be in ethanol: water extract s as a result it showed that the inhibitory effect increase as polarity increase	
*Rumexjaponicus**Houtt*. *(RJ)* (Root)	95% ethanol	Anti-inflammatory effects	*In-vitro* Human Keratinocyte HaCaT Cells (25 and 50 µg/mL)	Results showed that *RJ*has an anti-inflammatory effect by blocking mitogen-activated protein kinase (MAPK) and suppressing the activation of nuclear factor-kappa B (NF-κB) in tumor necrosis factor-α (TNF-α)	[12]
			In-vivo DNCB-Induced Atopic Dermatitis (4 mg/mL and 8 mg/mL RJ extract)	Results showed that topical administration of *RJ* in mice results in decreasing the severity of dermatitis as well as epidermal thickness and reduces mast cell and eosinophil infiltration in the skin and ear tissue	

Melasma is one of the most common skin disorders that affect facial areas when exposed to sunlight [13]. It is commonly appear as dark spots or patches on the skin face as a result of exposure to high ultraviolet (UV) light [13]. A cream for topical application that contains 1% *Rumexoccidentalis* extract is available in several countries in Asia and Europe which is considered a brand product to treat the facial hyperpigmentation [13]. Clinical studies have been conducted to investigate the safety and efficacy of a cream containing glycolic acid and *Rumexoccidentalis*[13], where the results showed that the *R. occidentalis*cream had a moderate effect in half of the patients as it does not completely remove the hyperpigmentation. The cream had no side effects apart from mild irritation [13].

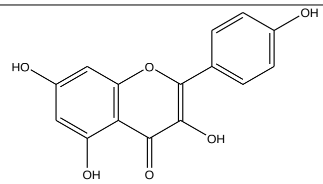
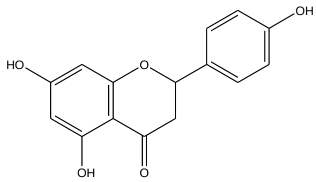
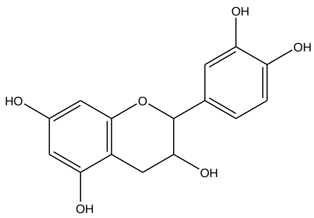
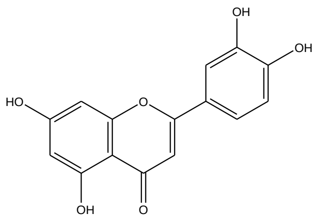
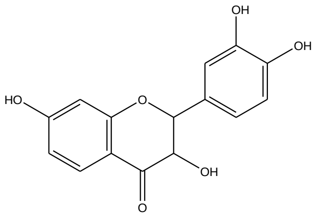
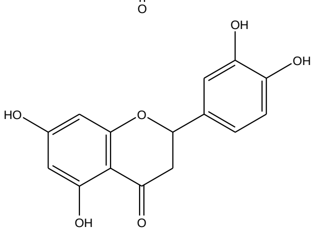
4. Bioactive compounds identified in Genus *Rumex*

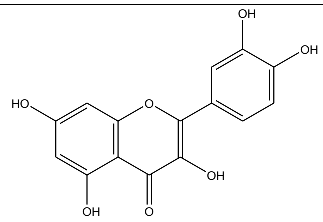
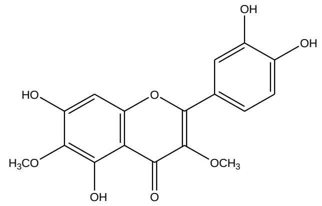
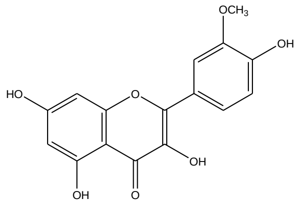
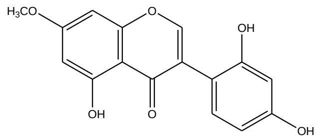
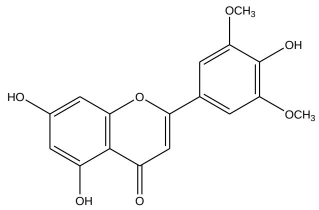
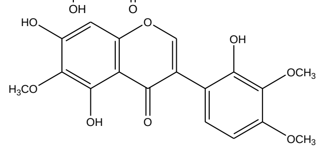
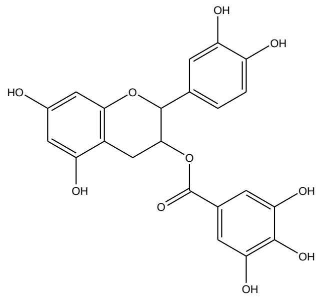
Recently, metabolomics has been applied for the identification and quantification of different classes of active constituents that have been discovered in *Rumex* species. One of the used techniques is the "untargeted" metabolomics technique such as ultra-performance liquid chromatography coupled with high-resolution mass-spectrometry (UPLC-MS), by utilizing this system in the negative ionization mode, many phytochemicals were identified in *Rumexcrispus* such as phenolic acids (2',6'-dihydroxy-4'-methylacetophenone), coumarins (scopoletin) and various anthraquinones. Moreover, investigation of the identified compounds in *Rumexcrispus*has shown that they have potential as anti-microbial activities against methicillin-resistant *Staphylococcus aureus* (MRSA) [14]. On the other hand, UPLC-DAD-ESI/MS technique was employed for the identification of the secondary metabolites in *Rumexnepalensis* such as flavonoids *viz.* quercetin-3-*O*-*β*-D-glucuronide, epicatechin-3-*O*-gallate, rutin, and kaempferol[15]. Also, the investigation of *Rumexvesicarius* extract using HPLC-PDA-ESIMS/MS in the negative ionization mode led to the identification and determination of different flavone and flavonol compounds such as 8-C-glucosyl-apigenin, 8-C-glucosyl-luteolin, 6-C-hexosyl-quercetin, and 3-*O*-rutinosyl-quercetin.These compounds were also found to possess many biological activities such as anti-oxidant and hepatoprotective activities [16]. *Rumex* species have been proven to have many biologically active compounds that have been a point of interest for researchers leading to the exploration of more *Rumex* species such as *Rumexhastatus*, *Rumexdentatus*, *Rumexcrispus*, *Rumexorientalis*, and *Rumexnepalensis* which have been found to contain polyphenolics such as rutin, kaempferol, naringenin and many stilbenes such as piceatannol, and resveratrol [17]. Whereas, *Rumextunetanus* flowers and stems extracts have been reported to contain various biologically active compounds, the most abundant of which were flavonol glycosides such as quercetin-3-*O*-glucuronide and quercetin-*O*-galloyl-hexoside, quercetin-3-*O*-rutinoside, and quercetin-3-*O*-glucoside that have been proven to have significant anti-oxidant activity [18]. In the following sections, we will have an overview of the compounds that have been identified in different *Rumex* species.

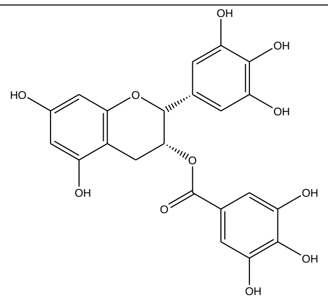
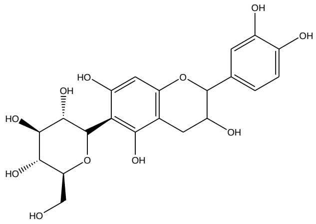
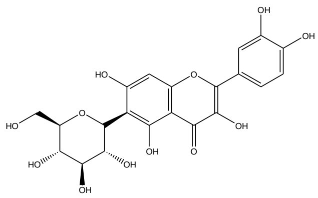
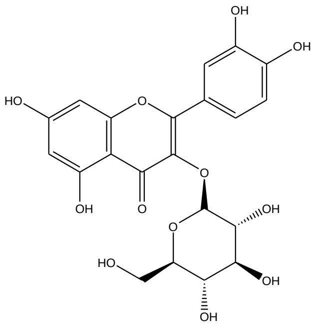
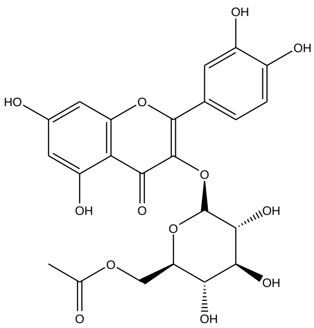
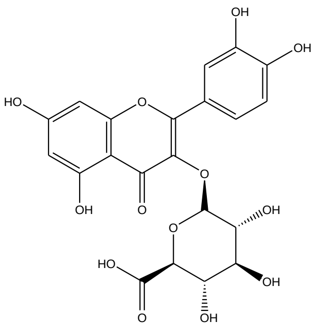
4.1 Flavonoids:

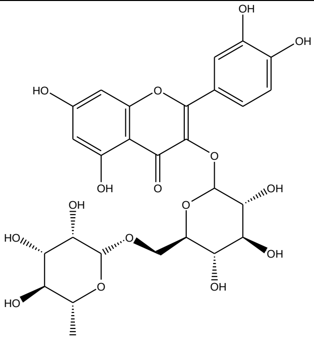
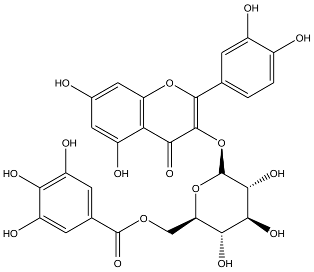
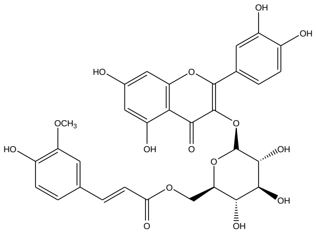
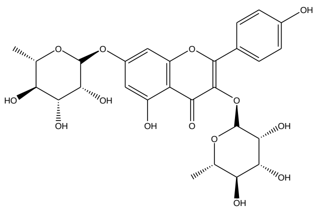
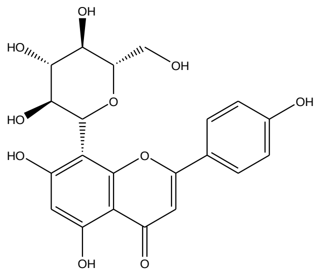
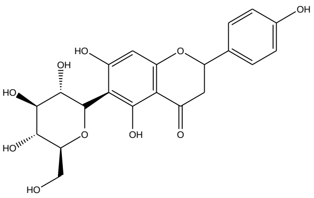
Flavonoids and their derivatives are considered one of the most important chemical compounds that attract the attention of many researchers due to their significant biological activities, especially as anti-oxidant and anti-inflammatory agents. Moreover, many flavonoids have been proven to possess anti-hypertensive, anti-diabetic, and gastro-protective activities against mucosal lesions, and many other related diseases[19, 20]. *Rumex*species are rich in flavonoids which were found in all parts of the plants. One of these species is *Rumexnepalensis* in which many flavonols and flavonol glycosides were identified using UPLC-DAD-ESI/MS in the roots and aerial parts, such as quercetin-3-*O*-*β*-D-glucuronide, rutin, kaempferol and kaempferol-3,7-dirhamnoside (**Table 3**)[15].

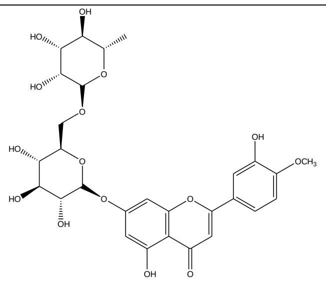
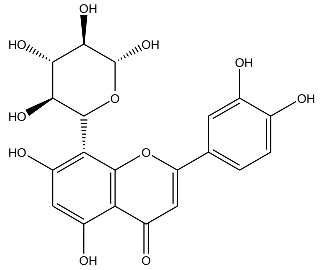
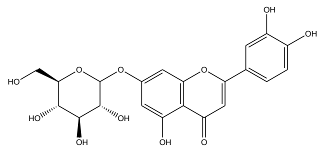
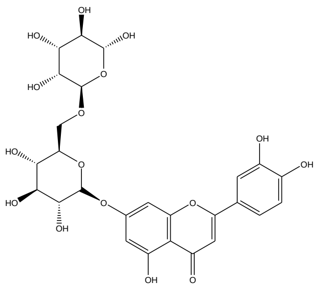
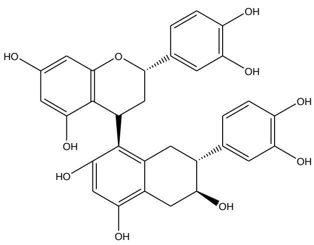
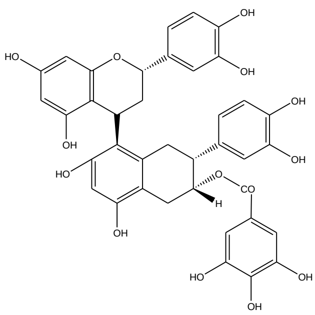
Table 3 : Flavonoids identified in Rumex species using LC–MS analysis

Compound name	**Chemical structure**	**Species**	**References**
Kaempferol		*R. nepalensis*, *R. crispus* L., *R. dentatus* L., *R. hastatus*D.Don, *R. nepalensis*Spreng, *R. orientalis*Bernh. exSchult.f.	[15, 50] [15, 17]
Naringenin		*R. crispus* L., *R. dentatus* L., *R. hastatus*D.Don, *R. nepalensis*Spreng, *R. orientalis*Bernh. exSchult.f. *R. tunetanus*	[17] [18]
Catechin/epicatechin		*R. vesicarius* L., *R. tunetanus*	[16], [18]
Luteolin		*R. tunetanus*	[18]
Fustin		*R. tunetanus*	[18]
Eriodictyol		*R. tunetanus*	[18]

Quercetin		*R. tunetanus*	[18]
Quercetin-3,6-dimethyl ether		*R. tunetanus*	[18]
Isorhamnetin		*R. tunetanus*	[18]
7-Methoxy-2`-hydroxy-genistein (Cajanin)		*R. tunetanus*	[18]
Tricin		*R. tunetanus*	[18]
3′,5,7-Trihydroxy-4′,5′,6-trimethoxyisoflavone (Irigenin)		*R. tunetanus*	[18]
Epicatechin -3-O-gallate/ catechingallate		*R. nepalensis*, *R. vesicarius* L., *R. tunetanus*	[15, 51] El-Hawary, Sokkar et al. 2011) [18]

Epigallocatechin gallate		*R. vesicarius* L.	[16]
6-C-Glucosyl-catechin		*R. vesicarius* L.	[16]
6-C-Hexosyl-quercetin		*R. vesicarius* L.	[16]
Quercetin-3-O-glucoside (I-III)		*R. tunetanus*	[18]
Quercetin-3-O-hexosyl-6¨-acetate		*R. tunetanus*	[18]
Quercetin-3-O-β-D-glucuronide		*R. nepalensis*	[15, 52]

Quercetin-3-O-rutinoside (rutin)		*R. crispus* L., *R. dentatus* L., *R. hastatus*D.Don, *R. nepalensis*Spreng, *R. orientalis*Bernh. exSchult.f. *R. vesicarius* L. *R. tunetanus*	(Wang, Wu et al. 2009, Sharma, Jandrotia et al. 2018[17][15] [16] Abidi, Ammar et al. 2019
Quercetin-O-galloyl-hexoside		*R. tunetanus*	[18]
Quercetin-O-feruloyl hexoside		*R. tunetanus*	[18]
Kaempferol-3,7-dirhamnoside		*R. nepalensis*	[15, 53]
8-C-Glucosyl- apigenin		*R. vesicarius* L.	[16]
6-C-Glucosyl- naringenin		*R. vesicarius* L.	[16]

7-O-Rhamno-hexosyl-diosmetin		*R. vesicarius* L.	[16]
8-C-Glucosyl-luteolin		*R. vesicarius* L.	[16]
Luteolin-7-O-glucoside (Cynaroside)		*R. tunetanus*	[18]
Luteolin-7-O-rutinoside (Scolymoside)		*R. tunetanus*	[18]
B-type procyanidin dimer (I-V)		*R. tunetanus*	[18]
B-type procyanidin dimer gallate (I-V)		*R. tunetanus*	[18]

Moreover, an investigation of the ethyl acetate and n-butanol fractions of the leaves of *Rumexvesicarius*using HPLC-PDA-ESIMS/MS in negative ionization mode resulted in the identification of 13-phenolic compounds some of which are flavonoids such as 8-C-glucosyl-apigenin, 8-C-glucosyl-luteolin, 6-C-hexosyl-quercetin, 3-*O*-rutinosyl-quercetin, 7-*O*-rhamno-hexosyl-diosmetin, 7-*O*-rhamno-acetylhexosyl-diosmetin, catechin, epicatechin, feruloylhexoside, 6-C-glucosyl-naringenin, epicatechingallate, 6-C-glucosyl-catechin, and epigallocatechin gallate (**Table 3**)[16].Furthermore, using LC-MS in positive mode for the determination of the metabolites in five different *Rumex* species which were *Rumexcrispus*, *Rumexdentatus*, *Rumexhastatus*, *Rumexnepalensis*, and *Rumexorientalis*, flavonoids such as rutin and kaempferol were identified[17]. Moreover, *Rumextunetanus*is one of the most important species having various bioactive compounds that were identified using RP-UHPLC-DAD-ESI-QTOF-MS and MS/MS, the flavonols content was estimated as 24% in the stems extract and 41.48% in the flowers extract represented by quercetin, quercetin-3-*O*-rutinoside, quercetin-3-*O*-glucoside, quercetin-3-*O*-glucuronide, quercetine-*O*-dihexoside, quercetin-3-*O*-hexosyl-6¨-acetate, quercetin-3,6-dimethyl ether and isorhamnetin**(Figure 1)**. Furthermore, the flavones content was estimated as 8.05% in the stems and 4.17% in the flowers represented by luteolin and luteolin glycosides as luteolin-7-*O*-rutinoside and luteolin-7-*O*-glycoside**(Figure 1)**. While, the flavanones content appeared as eriodictyol and naringenin, with 0.25% and 0.29% in the stems and flowers of *Rumextunetanus*extracts. Moreover, *Rumextunetanus*had 18.41% and 23.71% in the stems and flower parts, respectively, of flavanols such ascatechin and epicatechin. Whereas, the isoflavones were detected in a percentage of 1.33% and 0.51% in the stems and flower parts, respectively, and were represented by 7-methoxy 2'-hydroxy genistein and 5,7,4 -trihydroxy-6,3,5-trimethoxyisoflavone. Finally, flavonoid glycosides also have been identified and determined in *Rumex tetanus* where they constituted 0.29% and 1.37% in the stems and flower parts, respectively, such compounds as flavonoid glucoside-3-hydroxy-methyl-gutaroyl conjugate [18].

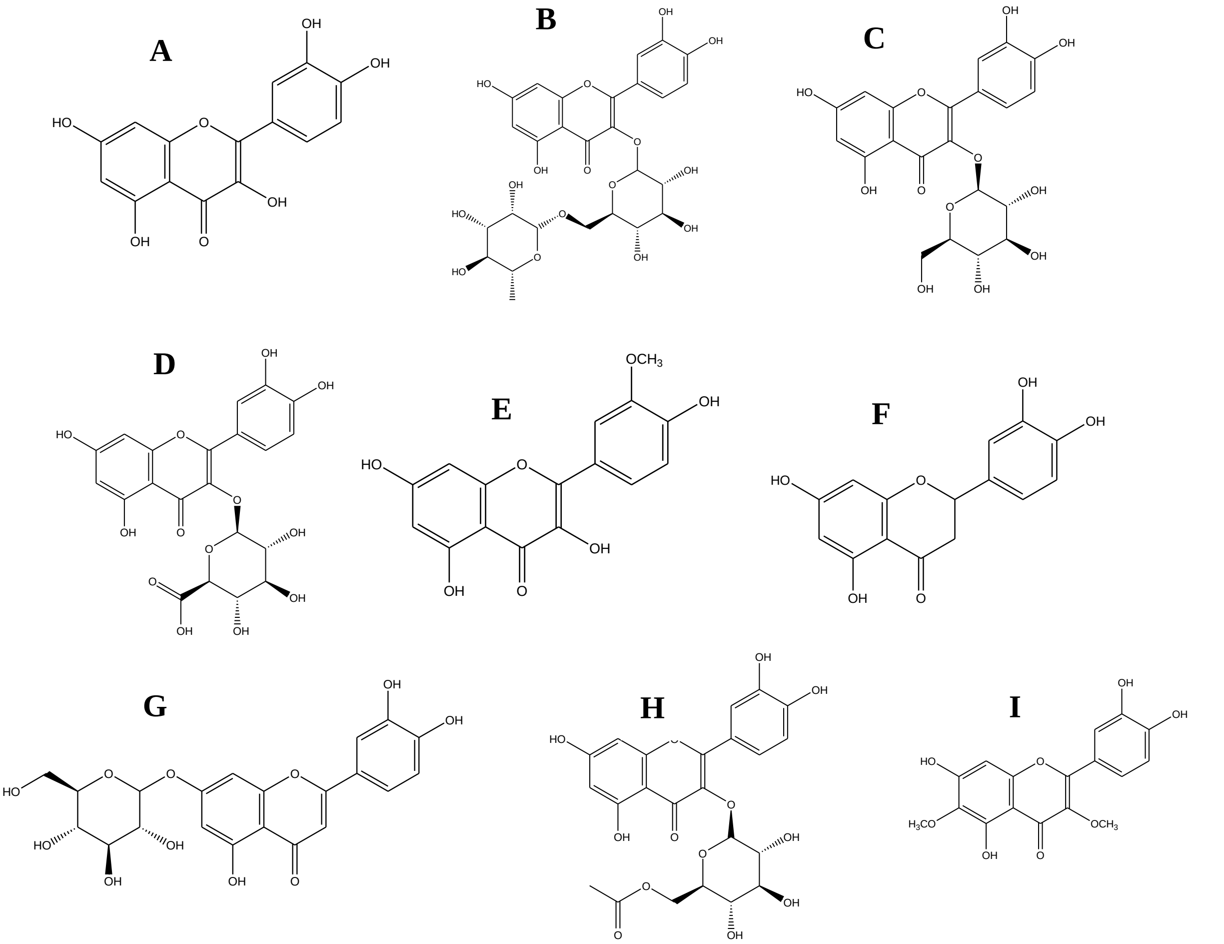
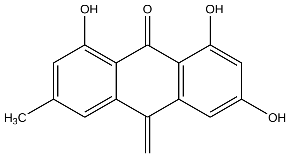
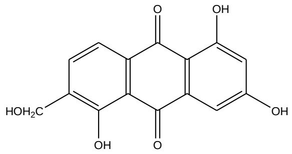
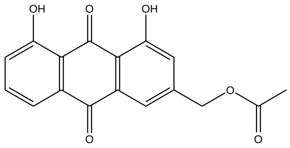
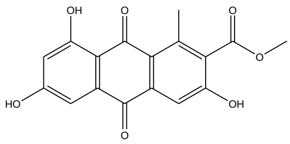
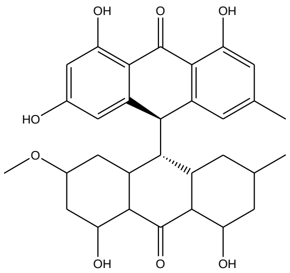
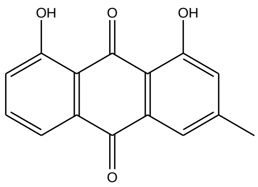
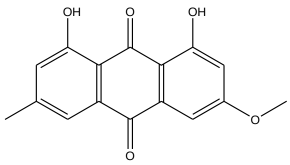


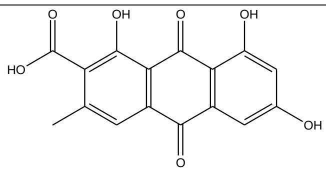
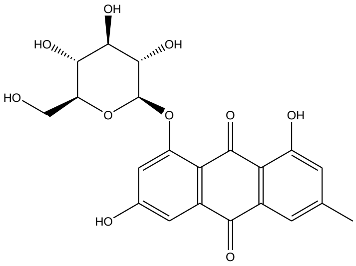
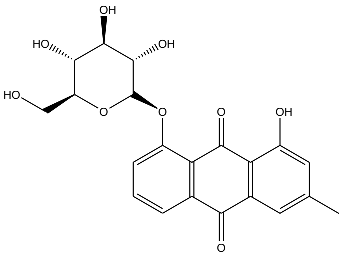
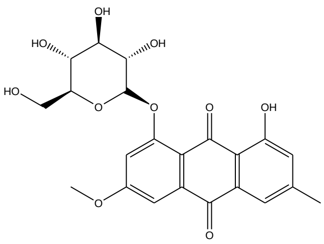
Figure 1. Structures of the major identified flavonoids in *Rumex* species, A: quercetin; B: quercetin-3-O-rutinoside; C: quercetin-3-O-glucoside; D: quercetin-3-O-glucuronide; E: isorhamnetin; F: eridictyol; G: luteolin-7-O-glucoside; H: quercetin-3-*O*-hexosyl-6¨-acetate; I: quercetin-3,6-dimethyl ether

4.2 Anthraquinone:

Genus *Rumex*is one of the largest genera that are rich in anthraquinones with its different types and derivatives depending on the investigated plant part. The roots of *Rumexcrispus* have shown to contain many anthraquinones such as 1,5-dihydroxy-3-methylanthraquinone and 1,5-dihydroxy-3-methoxy-7-methylanthraquinone**(Figure 2)**, these compounds have been proven to possess efficacy in the treatment of constipation as reported in the Turkish traditional medicine [20]. Recently, the anthraquinones and their derivatives have been found to have other pharmacological activities such as anti-inflammatory and purgative effects [21, 22]. Moreover, metabolomics analysis using (UPLC-MS) in the negative ionization mode has been used in the determination and identification of the major anthraquinones in the roots of *Rumexcrispus* extract such as emodin, 1,3,8-trihydroxy-6-methylanthraquinone, 1,3,5-trihydroxy-6-hydroxymethylanthraquinone, emodin-physcion (**Table 4)**. Also, it has been shown that the anthraquinones found in *Rumexcrispus* extract play a very important role as an anti-microbial agent against methicillin-resistant *Staphylococcus aureus* (MRSA) [14].While, it has been found that anthraquinones such asphyscion-8-O-β-D-glycopyranoside, chrysophanol-8-O-β-D-glycopyranoside, emodin, physicon, chrysophanol, endocrocin, and emodin-8-O-β-D-glycopyranoside have been detected and identified in the roots and aerial parts of *Rumexnepalensis*extractusing UPLC/MS (**Table 4)**[15].

Table 4: Anthraquinones identified in *Rumex species* using using LC–MS operating technique

Compound name	**Chemical structure**	**Species**	**References**
Emodin (1,3,8-Trihydroxy-6-methylanthraquinone)		*R. crispus* L., *R. dentatus* L., *R. hastatus*D.Don, *R. nepalensis*Spreng, *R. orientalis*Bernh. exSchult.f.	[54] [14, 55][15, 56]
1,3,5-Trihydroxy-6-hydroxymethylanthraquinone		*R. crispus*	[14, 57]
Aloe-emodin-ω-acetate		*R. crispus*	[14, 58]
Laccaic acid D methyl ester		*R. crispus*	[14, 59]
Emodin-physcion (syn. fallopion)		*R. crispus*	[14, 60]
Chrysophanol		*R. nepalensis*	[15, 56]
Physcion		*R. crispus* L., *R. dentatus* L., *R. hastatus*D.Don, *R. nepalensis*Spreng, *R. orientalis*Bernh. exSchult.f.	[15, 56]

Endocrocin		*R. nepalensis*	[15, 61]
Emodin-8-O-β-D-glucopyranoside		*R. nepalensis*	[56][62][15]
Chrysophanol-8-O-β-D-glucopyranoside		*R. nepalensis*	[15, 56]
Physcion-8-O-β-D-glucopyranoside		*R. nepalensis*	[15, 63]

Furthermore, physcion, and rhein**(Figure 2)**have been detected in *Rumexacetosa*, *Rumexacetosella*, *Rumexconfertus*, *Rumexcrispus*, *Rumexhydrolapathum*and*Rumexobtusifolius*[20]. Finally,emodin and physicon**(Figure 2)** identified in the positive mode of LC-MS were quantified to be employed for the discrimination of the different cytotypes of *Rumexcrispus*, *Rumexdentatus*, *Rumexhastatus*, *Rumexnepalensis*, and *R. orientalis* as shown in (**Table 4)**[17].

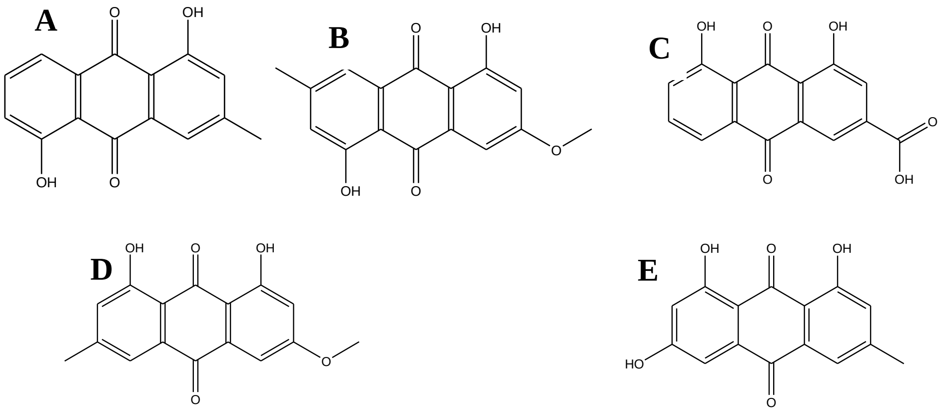


Figure 2. Structures of the major identified anthraquinones in *Rumex* species, A: 1,5-dihydroxy-3-methylanthraquinone; B: 1,5-dihydroxy-3-methoxy-7-methylanthraquinone; C: rhein; D: physcion; E: emodin

4.3 Chromones:

Moreover, *Rumex*species were found to have one of the interesting classes that is involved in many pharmacological actions which are the chromes that were found in *Rumexmaritimus*[20], such as 7-hydroxy-2,5-dimethyl chromone and 2-methyl-5-carboxy methyl-7-hydroxy chromone**(Figure 3)** that have been investigated for the treatment of diarrhea[23]. The roots and aerial parts of *Rumexnepalensis* were found to have aloesin**(Figure 3)** which is identified as chromone glycoside using UPLC-DAD-ESI/MS [15].

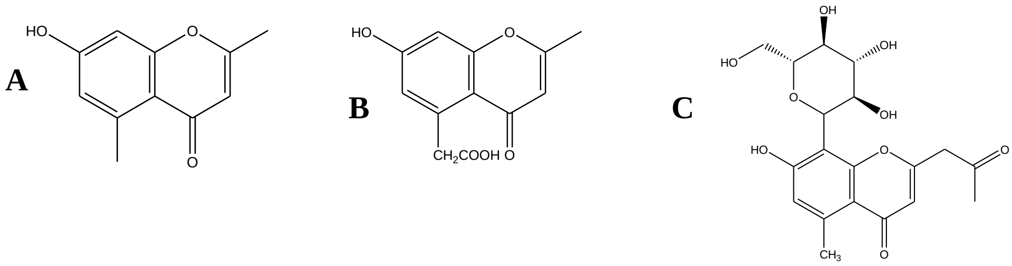


Figure 3. Structures of the major identified chromone in *Rumex* species, A: 7-hydroxy-2,5-dimethyl chromone; B: 2-methyl-5-carboxy methyl-7-hydroxy chromone; C: aleosin

4.4 Stilbenes:

Stilbenes is one of the phenolic classes included in *Rumex* species as polydatin**(Figure 4)** which was identified in *Rumexnepalensis*[15]. While, piceatannol and resveratrol **(Figure 4)** were found in five different *Rumex* species which were *Rumexcrispus*, *Rumexdentatus*, *Rumexhastatus*, *Rumexnepalensis,* and finally *Rumexorientalis*[17].

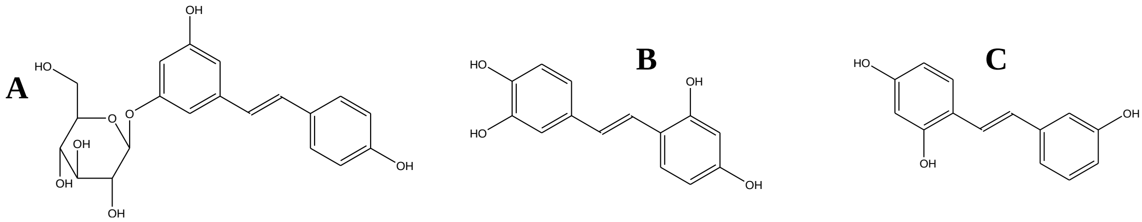


Figure 4. Structures of the major identified stilbene in *Rumex* species A: polydatin; B: piceatannol and C: resveratrol

4.5 Naphthalene derivatives

Naphthalene compounds are demonstrated to have many biological activities as laxatives, and treatment of diarrhea, and can be used as antiseptics [20].*Rumex* is one of the genera that are rich in naphthol compounds such as rumexoside, labadoside, and orientaloside which were detected in *Rumexpatientia*. Furthermore, *Rumexinduratus*wasfound to have other naphthol derivatives such as 1,1,6-trimethyl-1,2-dihydronaphthalene, 1,2-dihydroxy-2,5,8-trimethylnahthalene, 1,1,6,8-tetramethyl-1,2-dihydronaphthalene and 2,6-diisopropylnaphthalene which were reported to be used against insect attack [20]. *Rumexnepalensis* was found to have nepodin**,**torachrysone, and also rumexoside**(Figure 5)** as mentioned before in *Rumexpatientia* as mentioned in [15].

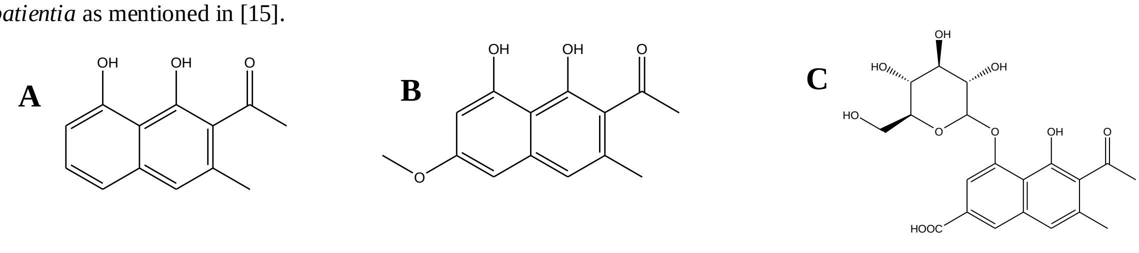


Figure 5. Structures of the major identified naphthalene derivatives in *Rumex* species, A: nepodin; B: torachrysone, and C: rumexoside

5. The mechanistic effect Rumex metabolites in preventing skin inflammation and aging

Exposure of the skin to UV radiation cause the activation of the family of protein kinases which includes protein kinase C delta (PKCδ) which activates the mitogen-activated protein kinase (MAPK) that is responsible for skin aging through the stimulation of nuclear factor kappa (NF-κB) and activator protein-1 (AP-1) that upregulate metalloproteinase (MMPs) and cyclooxygenase-2 (COX-2) causing degradation of the skin extracellular matrix (ECM) and inhibit collagen synthesis with the appearance of skin aging (**Figure 6**) [24]. On the other hand, Janus kinase 2/signal transducer and activator of transcription 3 (JAK2/STAT-3) is another pathway that causes skin inflammation [25].

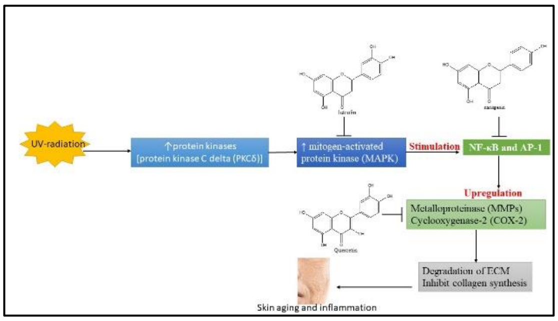


Figure 6. MAPK pathway of skin aging and the mechanism of action of some flavonoids

Several metabolites detected in the genus Rumex were reported to possess protecting and treating effects against various skin disorders and aging. Let us start with flavonoids, whose structure contributes to their antioxidant effect, especially the flavones and flavonols that possess a double bond between C2-C3 which has a radical stabilizing capacity, and the 4-keto group that chelates various metal ions such as iron and copper [26].

Luteolin is a flavone found both free and in the glycosidic form in various Rumex species, it was reported that luteolin modulates several inflammatory pathways such as mitogen-activated protein kinase (MAPK) and downregulates various genes such as TNF-α, NF-κB as well as interleukins 6 and 1β through its reducing reactive oxygen species and thus protect the skin against inflammation [27]. This was obvious when luteolin was tested on keratinocytes and fibroblasts and it inhibited the UV-induced release of pro-inflammatory cytokines IL-6 and -20 as well as metalloproteinases (MMP1) [28].

Likewise, quesrcetin which is the major flavonol identified in the genus Rumex also inhibited the UV-induced production of COX-2 and MMP-1 with the prevention of collagen degradation both in fibroblast and human skin through binding to Janus kinase-2 and protein kinase C (JAK2 and PKC δ [29].

Flavanones such as naringenin were also reported to inhibit the UV-induced production of TNF-α and interleukins (IL-1,-6,-10) in UV-induced skin damage in mice, this action was through downregulation of MMPs and NF-κB[30]. TNF-α, IL-1,-6,-10 are considered the most significant SASP (senescence-associated secretory phenotype) factors that convert the fibroblasts into pro-inflammatory cells which can promote the progression of cancer [26].

Similarly, the flavone apigenin can possess a protective effect against both skin aging and skin cancer through interaction with NF-kappa with subsequent inhibition of SASP factors [31]. It also exerts its protection against UVB-induced inflammation through suppression of IL-6 and -12 and overexpression of thrombospondin 1 (TSP-1) which is responsible for ECM organization and activity of matrix-degrading enzymes such as matrix metalloproteinases [32].

Rumex also is rich in flavans such as catechin and its derivatives. Catechin suppresses the TNF-α and prevents the accumulation of ROS and the activation of MAPK, Akt (protein kinase B), and, COX-2. It also inhibits the expression of cytokines such as IL-6 and -1β [33].

Anthraquinones also play an important role in protecting the skin, for example, emodin stimulates the synthesis of type-I collagen by enhancing the phosphorylation of 5`AMP-activated protein kinase in addition to its wound healing and anti-inflammatory activity [34]. Furthermore, aloe-emodin has a significant effect in regulating the gene expression of MAP kinases in fibroblasts [35]. Chrysophanol also was reported to play a remarkable anti-inflammatory role through inhibition of expression and phosphorylation of NF- κB and downregulate the pro-inflammatory cytokines such as TNF-α and IL1β [36].

The stilbenes such as piceatannol was also reported to possess antioxidant, skin whitening, blocks antiacne and wound healing effects [37]. Resveratrol is believed to possess its skin protecting effect through inhibition of phosphorylation of the protein servivin and its m-RNA, thus guard against the cell apoptosis. Blocking of NF-κB, cyclin D1, cyclin D2 and metalloproteinases, mitogen-activated protein kinase kinase (MAPKK) and mitogen-activated protein kinase (MAPK) [38]. The butyrate and isobutyrate derivatives of resveratrol have potent inhibitory effect on the inflammatory cytokines IL-6 and IL-8 and stimulate the synthesis of A1 collagen which in turns inhibit MMP-1 and 9 [38].

6. Statistical analysis:

The *in-vitro* and *in-vivo* results for all data included in our review are presented as mean ± S.E. Satistically analyzed using one-way analysis of variance (ANOVA) using Tukey's multiple range tests in Prism-5 (GraphPad Software Inc., La Jolla, CA, USA). The significant means level was analyzed by Duncan's *t*-test when p ≤ 5 [39, 40]. Metabolic profiling was done by using different techniques such as Mass Hunter Qualitative analysis and MZmine taking in consideration the molecular formula, error, Rt, and mass range as well as fragmentation pattern and compared to other literature reported [14, 18]

7. Conclusion

Aadvanced metabolomics techniques such as UPLC-DAD-ESI/MS, HPLC-PDA-ESIMS/MS, and UHPLC-DAD-ESI-QTOF-MS has been applied by many researchers on different *Rumex* species extracts for the determination and identification of active constituents that are important for *Rumex* pharmacological activitie. The major classes identified in the *Rumex*species were flavonoids and anthraquinones. Starting with flavonoids the most common class identified in *Rumex*species such as kaempferol and naringenin were well identified in *R. nepalensis*, *R. tunetanus*,*R. crispus* L., *R. dentatus* L., *R. hastatus*D.Don, *R. nepalensis*Spreng, *R. orientalis*Bernh. exSchult.f.. Catechin, Epicatechin, luteolin, luteolin-glucoside, quercetin and quercetin-glucoside were identified in *R. vesicarius* L., *R. tunetanus*. Moreover, Flavonoids possess several biologically active compounds that can be used as anti-cancer, anti-viral, anti-inflammatory, and anti-oxidant. The second largest class identified in *Rumex* species was the anthraquinones such as emodin and physcion one of the most common compounds detected in *R. crispus* L., *R. dentatus* L., *R. hastatus*D.Don, *R. nepalensis*Spreng, and *R. orientalis*Bernh. exSchult.f.. Endocrocin, chrysophanol, chrysophanol-glucoside, emodin-glucoside, and physcion-glucoside were identified in *R. nepalensis*. Furthermore, anthraquinones are well known for their important biological activities such as anti-cancer, anti-inflammatory, diuretic, anti-malarial, anti-fungal, and antibacterial. Skin aging is indeed an inevitable process that human beings must undergo affecting both function and appearance of the skin. Skin aging is mainly divided into two types. The first type,the intrinsic aging depends on time and genetic factors. While, the second type extrinsic aging depends on the environmental factors as subject to ultraviolet radiation. *Rumex*is important in delaying and reducing skin aging as it possesses anti-oxidant and anti-inflammatory effects. As reported *in-vitro* studies of *R. crispus*L. provide a powerful resource for delaying skin aging by inhibiting matrix metalloproteinase enzyme and having high SPF values and anti-oxidant capacities. Also, *Rumexnervosus* and *RumexjaponicusHoutt* showed powerful anti-inflammatory activities. Moreover, *Rumexpatientia*extracts showed high antioxidant activity. Finally, skin aging is one of the major problems that we face daily due to exposure to many environmental factors and UV radiation. Natural sources are one of the most common products that characterized by low side effects and low price compared to that of the synthetic products. Therefore, *in-vitro* and *in-vivo* biological studies of *Rumex*species need more investigation to be used as a potential source for delaying and preventing skin aging. As well as identifying *Rumex* active compounds is essential toshow their powerful correlation with anti-aging and many other biological activities.

7. **Conflicts of interest/Competing interests:** The authors have no conflict to declare

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