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Anticancer potential of *Rhus coriaria* L. (Sumac): A mini review

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ABSTRACT

Cancer is the biggest public health problem and the third leading cause of death in Iran. A healthy diet and daily consumption of natural antioxidants can help prevent cancer. Natural antioxidants have been recommended for a variety of health benefits due to their ability to scavenge free radicals, reactive derivatives, reducing oxidative stress and related damages. *Rhus coriaria* L. is rich in antioxidant compounds. Its anti-cancer effects have been documented in many *in vitro* and *in vivo* studies involving several cell lines and animal models. It inhibits carcinogens by inducing apoptosis, inhibiting cell proliferation, inhibiting oxygen species (ROS), and reducing tumour size. On the other hand, the high toxic effect of *R. coriaria* on cancer cells is associated with few or no side effects or damage to normal cells. Accordingly, this review provides an overview of recent advances in the use of *R. coriaria* against various types of cancer along with mechanisms of action. In addition, the present study summarizes *R. coriaria* as an anti-cancer agent and evaluates the potential of this natural compound as a complementary or alternative drug for cancer prevention and treatment.

Keywords: *Rush coriaria*, Sumac, Cancer, Antioxidant, Apoptosis.
Article type: Review Article.

INTRODUCTION

Rhus coriaria L. or Sumac belongs to the Anacardiaceae and distributed worldwide. It is traditionally used as a spice and flavouring for meat and salads (Akbari-Fakhrabadi *et al*. 2018). It also grows as a shrub (height 1 to 3 m) and has colourless leaves, red globular fruits with a single seed and small white-green flowers that are organized in clusters (Lo Vecchio *et al*. 2022). It is also used to treat diseases such as cancer (Al-Jaber *et al*. 2021). The bioactive compounds in *R. coriaria*, has an effect for antioxidant, anti-tumor, anti-microbial and anti-fungal activity, can be attributed to the therapeutic effects of this plant (Park *et al*. 2004; Abu-Reidah *et al*. 2014; Doğan *et al*. 2016). Evidence shows that this plant contains phytochemicals, such as phenolic and flavonoids compounds, isoflavones, tannins, anthocyanins, terpenoid, gallic acid, methyl gallate, kaempferol and quercetin (Hosseini *et al*. 2002). *R. coriaria* extracts at higher doses of 50 and 100 µg mL^{-1} induces apoptosis of cancer cells by increasing the activity of caspase-3 and Bax/Bcl-2 ratio, respectively (A Gabr *et al*. 2021). Studies have shown

that *R. coriaria* extract inhibits angiogenesis more effectively than pistachio extract (Mirian *et al*. 2015). This study focuses on the ability of this super-beneficial plant to prevent and treat various types of cancer. The aim of this study is an overview of anti-cancer studies published about *R. coriaria*.

MATERIALS AND METHODS

To conduct this review, databases such as WOS, PubMed, PMC, Scopus, ScienceDirect, and Google Scholar looked for articles on the role of sumac and its impact on different types of cannabis. Unrestricted tab of publishing keywords or keywords used separately in the title/ keywords/ abstract to retrieve articles include: Sumac, *Rhus coriaria*, herbal medicines, antioxidants and cancers. The retrieved articles were analysed once again. Only articles focusing on the effects of sumac and its derivatives on cancer control were analysed. A total of 35 articles were retrieved from databases. After analysis, 28 articles were deleted for the following reasons: reproducibility and obsolescence of articles, lack of abstracts and lack of access to their full text. Finally, 22 articles on the effect of sumac and antioxidant properties on cancer control were selected for review.

RESULTS

Anticancer perspectives of *Rhus coriaria*

A summary of the anticancer effects of sumac plant is detailed in Table 1.

Uterus, cervix, and retinoblastoma

Cervical cancer is the fourth most common cause of cancer deaths in women. Studies have shown that *R. coriaria* at non-cytotoxic concentrations of *R. coriaria* reduces the migration and growth of uterine cancer cells. *R. coriaria* methanol extract (31.25, 62.5 and 125 µg mL^{-1}) was also shown to have cytotoxic and anti-angiogenic effects against retinoblastoma Y79 cell line (Behrooeian *et al*. 2015). Thus, *in vitro* and *in vivo* studies are recommended to determine the anti-cancer effect of this herb against these cancer (Abdallah *et al*. 2019).

Breast cancer

The results of studies have shown that remedy of breast cancer cell lines (MDA-MB-231, MCF-7 and T47D) with dose of 50, 100, 200, 400 and 600 µg mL^{-1} *R. coriaria* ethanolic extract leads to DNA damage, G1 irreversible cessation and aging associated with β-galactosidase expression and dependently reducing time and concentration (El Hasasna *et al*. 2015). *R. coriaria* ethanol extract (10 and 50 µg mL^{-1}), significantly inhibits migration and invasion, blocks fibronectin adhesion, and also reduces metalloproteinase-9 (MMP-9) and prostaglandin E2 (Pg E2; El Hasasna *et al*. 2016). Similarly, ethanolic extracts of *R. coriaria* (50 or 150 µg mL^{-1}), inhibited angiogenesis in the chick embryo model by preventing the formation of capillary structures. It also inhibited the growth and metastasis of the MDA-MB-231 tumour (Al-Jaber *et al*. 2021). The anti-angiogenic potentials of *R. coriaria* methanol extract and pistachio in HUVEC cells were investigated exhibiting that *R. coriaria* methanol extract inhibits angiogenesis more effectively than methanol pistachio extract (Ghorbani *et al*. 2018). In addition, *R. coriaria* reduces inflammatory cytokines IL-6, TNF-α and IL-8, which seems to be the basic mechanism for the effects through inhibition of STAT3, NO and NF-κB pathways (El Hasasna *et al*. 2016). Quercetin is identified in *R. coriaria* through several mechanisms such as: induction of apoptosis, caspase-3 activation and mitochondrial dependence, inhibition of the AKT/MTOR pathway, as well as suppression of phosphorylation of regulated K1/extracellular signal kinases and its expression. It also reduces the number of tumours (metastases) and tumour volume (Reyes-Farias *et al*. 2019; Rauf *et al*. 2018). Therefore, it is suggested that quercetin, perhaps not only, contributes to the anti-cancer activity of *R. coriaria*. Hence, *R. coriaria* is identified as a promising candidate for prevention and treatment that modulates triple negative growth and metastasis of breast cancer.

Lung cancer

The results of studies have shown that aqueous, methanolic, dichloromethane and hexane extracts of *R. coriaria* have strong anti-cancer and cytotoxic activities depending on time and dose. Among the extracts, aqueous and methanol extracts with IC_{50} values in the range of 5.08 - 6. 49 µg mL^{-1} are highly cytotoxic against lung cancer. It has also been observed that cell growth and viability are inhibited by extracts. In addition, increasing

the time and dose of exposure to *R. coriaria* extract leads to the elevated lysosomal function and membrane permeability in cell lines (Gezici 2019).

Colon cancer

Cancer treatment depends on the extent of the spread, the type of cancer, age, health status and individual characteristics (Rauf *et al*. 2018). Several studies have examined the effect of *R. coriaria* on colon cancer. *R. coriaria* in colorectal cancer activates both programmed cell death pathways through stimulation of the ubiquitin protein and the ubiquitin proteasome system (UPS). Athamneh *et al.* (2017) investigated the anti-cancer effect of *R. coriaria* ethanolic extract (0, 75, 150, 300, 450 and 600 µg mL^{-1}) on two colorectal cancer cell lines, HT-29 and Caco-2. The results of this study showed that *R. coriaria* reduced cell viability, cell colony growth, inhibited HT-29 and reduced HT-29 tumour growth in vivo using mouse Xenograft transplantation. Finally, the role of *R. coriaria* in colorectal cancer was mediated using proteasome inhibitors (Athamneh *et al*. 2017). Medicinal plants exhibit therapeutic effects on cancers due to their chemical, medicinal and antioxidant compounds (Khan *et al*. 2017; Muazzam *et al*. 2018; Kubatka *et al*. 2020; Suhad *et al*. 2021; Khademian Amiri *et al*. 2022; Shahsavari *et al*. 2022; Mohammadrezaei Khorramabadi *et al*. 2022; Murad *et al*. 2022; Mustafa *et al*. 2022). Many chemical compounds can cause lesions in body organs, especially the occurrence of cancer (Shalmani *et al*. 2015; Manouchehri *et al*. 2021; Manouchehri *et al*. 2021), so the use of substances, natural antioxidants and medicinal plants are an important approach in preventing the occurrence of many diseases (Hasanvand *et al*. 2019; Darvishi *et al*. 2022; Altememy *et al*. 2023; Amiri *et al*. 2023).

Table 1. Anticancer perspectives of *Rhus coriaria*, along with mechanisms of action.

Cervix Cancer	*R. coriaria* at non-cytotoxic concentration inhibited the advancement of HeLa cell of uterus cervix cancer.	(Abdallah *et al*. 2019)
Breast cancer	*R. coriaria* inhibits the survival of cells of breast cancer. Also, the extract caused aging in triple negative breast cancer cells by activating p38 and ERK1/2 pathways.	(El Hasasna *et al*. 2015)
Breast cancer	*R. coriaria* inhibited the cell cycle and significantly prevented invasion and migration of angiogenesis, blocked fibronectin adhesion, and reduced MMP-9 metalloproteinase and prostaglandin E2. In addition, they decreased the inflammatory alpha cytokines such as IL-6, IL-8 and TNF-α.	(El Hasasna *et al*. 2016)
Breast cancer	AgSu / NPs synthesized with extract of *R. coriaria* reduced cell viability and induced apoptotic cell death in the MCF-7 breast cancer cell line.	(Ghorbani *et al*. 2018)
Breast cancer	Plant of *R. coriaria* (Methanolic extract) caused an increase in caspase-3, Bax, and Bax / Bcl-2 expression in rat model of breast cancer	(Kubatka *et al.* 2020)
Breast cancer	*R. coriaria* showed anti-breast cancer activity by suppressing metastasis, angiogenesis and tumor growth by inhibiting STAT3, NF B and nitric oxide pathways.	(Al-Jaber *et al*. 2021)
Colon cancer	The ethanolic extract of *R. coriaria* fruit showed anti-colon cancer activity by stimulating proteasome activity and inducing autophagy cell death and apoptosis of cell lines in HT-29 and Caco-2.	(Athamneh *et al*. 2017)
Lung cancer	Sumac extract inhibited the proliferation of lung cancer cells A549, H1299 and (H460)	(Gezici 2019)

CONCLUSION

R. coriaria has a good activity in reducing the effects of free radicals due to its potential antioxidant power. However, more research are needed on this medicinal plant. In addition, since most of the findings in the present study are based on laboratory and animal, which do not necessarily reflect the effects of *R. coriaria* in humans, further research involving various pharmacokinetic parameters in the future, before this substance enters into action be recommended.

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