Sanguinaria Canadensis: Sanguinarine Containing Potent Medicinal Roots and Rhizomes of Broad Antimicrobial and Anti-Inflammatory Activities

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Abstract: *Sanguinaria canadensis,* is a western medicinal roots and rhizomes. The plant is widely distributed in Canada and United states. Sanguinarine, a quartenary ammonium major alkaloid of *Sanguinaria*, has broad antimicrobial as well as anti-inflammatory properties. Its dried roots and rhizomes are popular for its emetic and expectorant properties and remarkably used as antimicrobial agent. Sanguinarine is widely used commercially in toothpastes and mouthwashes as an antiplaque agent. Crude methanolic extract of red root showed antithrombin, antimicrobial and antimycobacterial activities and its potent activity against *Mycobacterium aurum*, with MIC values of 62.5 µg/mL proved it a valuable anti-tubercular drug. Chelerythrine chloride was the most active among all with IC_{50} value of 14.3 µg/mL against *M. bovis* BCG. Inhibition of Collagenase and bone resorption has been documented, *invitro. Sanguinaria canadensis* exract and *Sanguinaria* alkaloids were also tested against *H. pylori* with significant activity. Its burning capability is used in Homeopathic system of medicine and is indicated there in the ailments of respiratory tract. Sanguinarine has a use in reducing dental plaque and gingivitis and this use is accepted by FDA. In low doses the use of these alkaloids is safe and therapeutic but they are toxic at higher doses.

Keywords: *S. canadensis,* Sanguinarine, Chelerythrine chloride, Antimicrobial, Anti-inflammatory, Anti-tubercular drug, *Mycobacterium aurum, H. pylori,* Homeopathy.

INTRODUCTION

Sanguinaria canadensis, a western plant also called as bloodroot. Plant belongs to family Papaveraceae Juss {Genera Plantarum 235–236. 1789. (4 Aug 1789) (Gen. Pl.)}, a family of 26 genera and nearly 200 species, distributed mostly in temperate and subtropical regions of northern hemisphere, including western north America and eastern Asia. Only 7 genera and 22 species of *Papaveraceae* have been reported from Pakistan [1]. The plant is widely distributed in Canada and United states. *Sanguinaria australis* Greene *Sanguinaria canadensis* var. *rotundifolia* (Greene) Fedde and *Sanguinaria dilleniana* Greene are the synonyms of the plant. Its english names are Bloodroot, Coon root, Red-puccoon, Sanguinaria, Tetterwort, Red root, Indian paint and Red Indian Paint. The Canadian bloodroot is a perennial with a woody, creeping rootstock containing a reddish juice. Each year the rootstock produces a single palmate leaf with seven crenate, serrate lobes and a hairless stalk which can be up to 25cm in height and bears a single white flower. The upper surface of the leaf is yellow-green; the lower surface is lighter and has conspicuous orange to violet veins. The flower has 8 to 10 petals and numerous stamens. Two carpels grow together to form a many-seeded capsule that can be between 3cm and 5cm in length (Figure **1**) [1, 2].

Traditionally, Native Americans used blood root to paint their bodies while, medicinally, Sanguinarine (Figure **2**) showed anti-inflammatory, antimicrobial and antiplaque activities. Due to its ability of inhibiting bacterial adherence in dental plaque and broad antimicrobial activities, it showed antiplaque action against dental plaque and thus it has been considered to be formulated in a slow release polymer system to be used for treating periodontitis [20-26].

PHARMACOLOGICAL ACTIVITIES

Antimicrobial Activity

Plant *Sanguinaria* also contains benzophenanthridine alkaloid that is sanguinarine (Figure **2**) which showed antifungal action on infected chronically inflamed vagina when used in a composition with extract of *Zanthoxylurn bungeanum or Echinacea angustifolia* [5]. Sanguinarine also inhibited MRSA (Methicillin resistant *S. aureus*) by deformation in septa and predisposition of cell lysis [3].

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S. canadensis also have fungicidal activity against fungal diseases of plants [6]. In addition, *Sanguinaria canadensis* exract and *Sanguinaria* alkaloids were also tested against *H. pylori* with significant activity [12].

Antitubercular and Leprostatic Activity

Crude methanolic extracts of forty three plants were tested for their anti-mycobacterial and leprostatic activity. Methanolic extract of roots and rhizomes of *Sanguinaria canadensis* (% yield = 27.10) was found to be effective against *Mycobacterium aurum* and *Mycobacterium smegmatis,* with an MIC values of 62.5 µg/mL and > 500 µg/mL, respectively. Thus, potent activity against *Mycobacterium aurum* proved it a valuable anti-tubercular drug. Among all the plant extracts, *Sanguinaria canadensis* extract was found to be one of the most potent extract. Bioassay guided fractionation produced two alkaloids, sanguinarine and chelerythrine chloride. Chelerythrine chloride is found to have potent activity as an anti-tubercular agent with the IC_{50} values of 7.30 µg/mL [19.02 µM] and 29.0 µg/mL [75.56 µM] when tested against *M. aurum* and *M. smegmatis*, respectively. In the same study, sanguinarine showed significant IC_{50} value of 9.61 µg/mL [26.19 µM] against *M. aurum* which was very close to Chelerythrine chloride and it has an IC_{50} value of 41.18 µg/mL [112.21 µM] against *M. smegmatis*. It was noted that antimicrobial activity of both the compounds have four fold decrease in activity when tested against *M. aurum* as compared to *M. smegmatis*. Buckachiol also showed activity against *M. aurum* and *M. smegmatis*. All the three compounds have significant activity against *M. bovis* BCG comparable to their activity against *M. aurum*. Chelerythrine chloride was the most active among all with IC_{50} value of 14.3 µg/mL [37.3 µM] against *M. bovis* BCG [4].

Sanguinarine, a Potent Antiangiogenic Substance

Sanguinarine was proved as a potent antiangiogenic substance and claimed its importance in the search of novel antiangiogenic compounds. Although, Sanguinarine is known for its antimicrobial properties and effectively is being used in toothpaste and oral rinses as antiplaque and anti-inflammatory and the concentration claimed to be antimicrobial is in the range of micromolar but here the concentration range was found to be in nanomolar(nM) range and the compound showed its antiangiogenic activity in dose dependent manner. So it was suggested to test the novel compound in lower doses to avail its best suited antiangiogenic dose [7]. Basini *et al*. 2007 proposed the mechanism of angiogenesis inhibiting activity of sanguinarine that it suppressed basal and VEGF-induced new vessel growth [8].

Inducing Apoptosis in Carcinoma

Despite of other remarkable activities, Sanguinarine was proved to have the indispensable ability to inhibit growth of human squamous carcinoma (A431) cells having the mechanism of action of induction of apoptosis [9].

Antitumor Agent

In a study testing a large number of herbs (374) which were extracted in absolute ethanol and tested in the concentration range of 10 µg/mL to 5 mg/mL for their dose-dependent tumoricidal effects using immortal neuroblastoma of spontaneous malignant tumor cell lines *in vitro*, amazingly blood root was found to have second lethal herb among all. Its LC_{50} value comes to 0.04mg/mL Sanguinaria contains sanguinarine and berberine, the two alkaloids considered toxic; this may be a reason of its anticancer activity [10].

Figure 1: Medicinal herb: *Sanguinaria Canadensis.*

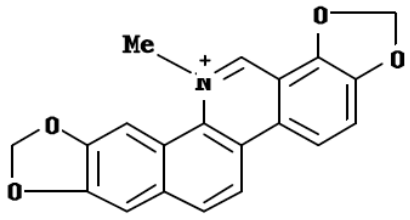

Figure 2: Structure of Sanguinarine.

CLINICAL USE

Homeopathic Metria Medica

Its burning potential was used in Homeopathic system of medicine and is indicated there in the ailments of respiratory tract including tonsillitis, pharyngitis, whooping cough, dry cough, influenza and also indicated in menopausal hot flashes, migraines and throbbing headaches that settle over right eye [18].

Oral Rinses and Toothpastes

Sanguinarine, a quartenary ammonium major alkaloid of Sanguinaria, has broad antimicrobial activity as well as anti-inflammatory properties. *In vitro* studies indicated that the anti-plaque action of sanguinarine is due to its ability to inhibit bacterial adherence to newly formed pellicle, its retention in plaque being 10-100 times its saliva concentration, and due to its antimicrobial properties [20]. A clinical comparison of the effects of chlorhexidine, phenolics, and sanguinarine on dental plaque and gingivitis showed that sanguinarine showed moderate, yet significant, reductions in plaque compared to placebo [21]. In another study on sanguinarine (Figure **2**) also showed that it had a high specificity and retention in dental plaque [22]. Moreover, tooth paste and oral rinses containing its extract has been tested clinically and the results showed that dentifrices containing sanguinaria extract decreased gum inflammation and had antiplaque action in orthodontic patients [23]. In addition, toothpastes and oral rinses containing its extract was also evaluated when it is used in combination with zinc chloride and fluoride. The clinical efficacy and safety was good when sanguinaria extract was used with the combination of zinc chloride, but the preparation did not show to improve the growth of opportunistic microflora in the oral cavity while the gingivitis decreased in the active group [24, 25]. In a study comparing the effects of sanguinaria extract with or without fluoride, it was manifested that the combined effect of sanguinaria and fluoride was better than the placebo [26]. In addition, in a combined regimen using its extract after tooth scaling and root planning it was found to be beneficial in a short term study [28]. But, in another clinical study evaluating the efficacy of dentifrices containing sanguinaria extract in improving gingival inflammation after initial periodontal therapy in a short term study, it was found no better than placebo [27].

Natural Appetizers

A review by Sarah Mellor, discussing plant natural appetite enhancers, confer the use of sanguinarine in addition to other natural appetite stimulants [31].

Wound Healer

Sanguinaria is one of the plants that are widely used for the topical application in healing of wound and as anti-aging agent [32].

Menopausal Indication

A clinical observational study by Bordet *et al*., 2008, and a RCT [29, 30] proved the significance of homeopathic medicine containing S*anguinaria canadensis* in reducing hot flashes in menopausal women.

PHYTOCHEMISTRY

Quaternary benzo[c]phenanthridine alkaloids are widely spread in *Sanguinaria canadensis*. Sanguinarine is one of them [11]. *Sanguinaria canadensis* contains quaternary benzo[c]phenanthridine alkaloids in its underground part *i.e*. sanguinarine , chelerythrine, chelirubine, chelilutine, sanguilutine, sanguirubine and macarpine [13]. In addition, protopine, alpha- beta-allocryptopine, sanguilutine, oxysanguinarine, sanguidimerine, coptisine and homochelidonine were also found. Resins, starch, citric and malic acids were also present [14] (Table **1**).

Table 1: Phytochemicals in *Sanguinaria spp*

Str. #	Name	Molecular Formula
1	Chelerythrine	$C_{21}H_{18}NO_4^+$
2	Chelerythrine; 12-Methoxy	$C_{22}H_{20}NO_5^+$
3	Chelirubine	$C_{21}H_{16}NO_5^+$
4	Dihydrobenzophenanthridine oxidase	
5	Dihydrosanguilutine	$C_{23}H_{25}NO_5$
6	Dihydrosanguinarine; 8-Oxo	$C_{20}H_{13}NO_5$
7	Fagarine I	$C_{21}H_{23}NO_5$
8	Isohypocrellin	$C_{30}H_{26}O_{10}$
9	Protopine	$C_{20}H_{19}NO_5$
10	Sanguidimerine; (8*R**,8'*R**)-form	$C_{43}H_{32}N_2O_9$
11	Sanguilutine	$C_{23}H_{24}NO_5^+$
12	Sanguinarine	$C_{20}H_{14}NO_4^+$
13	Sanguirubine	$C_{22}H_{20}NO_5^+$

TOXICOLOGY

In an attempt of finding new algicide and cyanocide, aqueous extract of roots and rhizomes of *Sanguinaria canadensis* showed significant toxicity against aquatic organisms [15]. In another study, by the same authors as in this research, concentrated homeopathic mother tincture (hydro-ethanolic extract) of *Sanguinaria* and *Aloe vera* gel was tested for toxicity, in which *Sanguinaria* showed significant activity with 0.021 mg/mL LD_{50} against *Artemia salina* [16]. In addition, the acute oral, intravenous and dermal toxicity of sanguinarine and of two alkaloid extracts of *Sanguinaria canadensis* L. was determined in animal models. 1440 mg/kg and 1250 mg/kg were the values of LD_{50} in rats of the two alkaloid extracts, respectively, while the sanguinarine is relatively safe with the oral LD_{50} values of 1658 mg/kg. Intravenous toxicity of sanguinarine was determined to be 29 mg/kg in rats which showed that the pure compound is more toxic. While feeding the rats with the sanguinarine in the dose of 150 ppm for forteen days and with the dose of 0.6 mg/kg body weight for thirty days, no signs of toxicity were observed. The acute dermal toxicity of sanguinarine in rabbits was found to have the LD_{50} values greater than 200mg/kg body weight [17]. Sanguinarine leads to nausea, vomiting and severe burning pain in stomach and in large doses can be fatal [18]. Commercially, sanguinarine has been used in a number of the oral hygiene formulations, one of them was banned due to its risk of developing leukoplakia [19].

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