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Aradhana Goswami
Research Scholar, Department of Botany, SGS Government PG College, Sidhi, Madhya Pradesh, India

IP Kumhar
Professor, Department of Botany, SGS Government PG College, Sidhi, Madhya Pradesh, India

M Salim
Retd. Professor and Head, Department of Botany, SGS Government PG College, Sidhi, Madhya Pradesh, India

Corresponding Author:
Aradhana Goswami
Research Scholar, Department of Botany, SGS Government PG College, Sidhi, Madhya Pradesh, India

Traditional medicinal use of *Hibiscus rosa* (Holyhock)

Aradhana Goswami, IP Kumhar and M Salim

Abstract
The genus *Hibiscus rosa* (Hoylyhock) consists more than 40 subspecies. Most of them were partly studied but some of them were not. In this review we will introduce the traditional medicinal knowledge and uses of this genus, summarize and discuss the modern research reports of the medicinal/biological activities of the various subspecies. Special attention will be paid to *Hibiscus rosa*, the most investigated subspecies of this genus. Clear emphasis will be laid upon some reported natural products isolated from subspecies of Holyhock. Future possible studies will be suggested.

Keywords: Traditional, Medicinal uses, *Hibiscus rosa,* Holyhock

Introduction
Holyhock is a genus of flowering plants known for their large and colorful blooms, considered to be very striking. The Barcode of Life Data Systems indicates that this genus is originally from Asia and Europe (Ratnasingham and Hebert, 2007) [1]. The number of subspecies that consist this genus is not definite, and it varies from 21 according to the "U.S. National Plant Germplasm System", to 40 subspecies, (Joharchi *et al.* 2012) [2] and even higher in some reports.
Most of the subspecies can be found in Asia, especially in Iran (34 ssp.) and Turkey (18 ssp.) Badrkhani *et al.* (2014) [3] and Uzunhisarcikli, *et al.* (2012) [4]. Humans have taken this genus with them, mainly Holyhock, while migrating to the "New World", and with the plants, the traditional medicine uses of them were also adopted.

Traditional uses of Holyhock subspecies
The various subspecies of this plant genus have been utilized by the people of Eurasia since ancient times. About 60000 years ago, the extinct Neandarthal humans used *Hibiscus rosa* for medicinal and ritual reasons (Cowan, 1999) [5].

Biological and medicinal activities of Holyhock subspecies
The medicinal and biological effects of the Holyhock subspecies are diverse and include antioxidant, antimicrobial, antiviral, hepatoprotective properties, among others. Along with that, it is interesting to notice some reports of last few years that present modern uses, such as nanomaterials synthesis (section 4). However, it is important to point out that these actions do not involve substances that affect the mind or alter the psyche, such as those found in plants or their extracts. This can be attributed to the minimal presence of alkaloids and similar compounds in the specific type of Holyhock, which have not been shown to have harmful effects on humans or other animals.

Biological and medicinal activities of Holyhock
Hibiscus rosa is the most researched subtype of Holyhock. Many of the biological and medicinal properties listed in table 1 for other studied subtypes of Holyhock are also documented in publications concerning Hibiscus rosa. The chemical makeup of Hibiscus rosa has been thoroughly examined, and although not fully understood, some of its components have been extensively tested for medicinal and biological effects. Apart from its traditional medicinal applications, Hibiscus rosa has also been utilized in the traditional dye industry and, more recently, in the field of Nano chemistry. Summary of research articles of *Hibiscus rosa* properties are shown in Table 1.

Discussion and Future Opportunities

Antioxidant activity was reported for some subspecies of *Hibiscus rosa* (Ammar *et al.* 2013, Liu *et al.* 2014 and Abd El-Salam *et al.* 2016) [6-8]. Numerous research studies have shown two significant findings. Firstly, polyphenols are the primary group of compounds responsible for the antioxidant properties. Secondly, the antioxidant capacity of extracts from various parts of these plants may differ, but all exhibit strong antioxidant abilities.

Table 1: Summary of research articles on *Hibiscus rosa*

Properties	Active Materials / Mode of Action
Fatty acids changes Coloring, pigmentation	During the plant's lifespan, there are variations in the types of fatty acids present, with Althaein, a blue pigment, making up 11% of all pigmentation. Anthocyanins, which are red dyes used for food coloring, constitute 75% of the pigmentation. The chemical structure of the 12 compounds responsible for giving *Hibiscus rosa* its color has been identified. (var. nigra) its color (Hosaka *et al.* 2012) [9].
Nanochemistry uses	Ethanolic extract serves as an affordable, natural sensitizer for the production of strontium-titanate nanoparticles (Gholamrezaei *et al.* 2016) [10]. Silver nanoparticles (AgNP's) were prepared and used as antimicrobial agents. AgNP's were prepared by reduction of $AgNO_3$ by aqueous extract of the plant (Ebrahiminezhad *et al.* 2016) [11].
Chemical composition	Acidic polysaccharides were isolated and identified (compared with *Malva sylvestris*) Classen and Blaschek, (1998) [12]. Acidic polysaccharide, rhamnoglucouronan, was isolated from the stems of the plant and analyzed (Atkhamova *et al.* 2001) [13]. Phenolic acids (ferulic, vanillic, syringic, p-coumaric, p-hydroxybenzoic, p-hydroxyphenylacetic and caffeic) were identified and determined quantitively (Dudek *et al.* 2006) [14]. Partial chemical composition: some metals, amino acids and monosaccharides were identified and quantified (Azizov, *et al.* 2007) [15]. Mercury accummulation in roots introduced compared with other plants in Poland (Ordak, *et al.* 2016) [16]. Pictinic polymers (water and alcohol insoluble) from the flowers were isolated and analyzed to result mainly rhamnoglucogalacturonan, that consists rhamnose, glucorunic and galactorunic acids (Rakhimov, *et al.* 2007) [17]. Two new compounds from ethanolic extract (Cheng, *et al.* 2013) [18]. Isolation and identification of 17 known compounds (Rakhmatova, *et al.* 2015) [19]. Sono-assisted extraction of alcohol-insoluble compounds that yielded mainly high molecular weight polymers like peptides and polysaccharides (acidic) Eskandari and Samavati (2015) [20].
Antibacterial/Antimicribial/ Antifungal	Evaluation of antimicrobial and cytotoxic properties of extracts obtained from n-hexane, ethanol, methanol, ethyl acetate, and water against ten different bacterial species and the Candida albicans fungus was conducted (Mert *et al.* 2010) [21]. Ethanolic extract activity against nine bacteria species (Seyyednejad, *et al.* 2010) [22]. Water-ethanol (50%) extract found active against Streptococcus pneumoniae and Klebsiella pneumonia (Ghasemi, *et al.* 2016) [23].
Antioxidant	The antioxidant effect of the methanolic extract was evaluated through DPPH with an examination of the phenolic compounds and saccharides through chemical analysis. (Ammar, *et al.* 2013) [6]. Antioxidant activities of water, ethanol, butanol and chloroform extracts of the seeds were measured by three different methods and phenolic content was identified and quantified (Liu, *et al.* 2014) [7]. Aqueous mixture of polyphenols was force fed to rats and the animals were forced to swim to exhaustion. These animals showed longer swimming time compared to control. This was confirmed by tests of various metabolites. Kaempferol and its 3-glucoside (astragalin) contained in ethanolic extract have strong antioxidant activity (Abd El-Salam *et al.* 2016) [8].
Anticancer	Kaempferol and its 3-glucoside (astragalin) contained in ethanolic extract have strong anticancer activity (Abd El-Salam *et al.* 2016) [8]. Antiproliferative activity of methanolic extract against rat brain tumor and human cervix carcinoma cell lines compared with 5-florouracil and cisplatin (control) Yaglioglu, *et al.* (2016) [24]. Ethyl acetate seed extract inhibits the growth of stem cell driven colon cancer cells *in vitro* and antagonize the growth of tumor xenografts *in vivo* (Ahmed, *et al.* 2016) [25].
Antiviral	80% Aqueous methanolic extract with anti-HIV activity (Asres, *et al.* 2001) [26]. Aqueous and ethanol extracts were tested for acyclovir-resistant Hsv type-1 in cell culture (Shoeib, *et al.* 2011) [27].
Immunomodulatory	Aqueous extract is B-lymphocyte polyclonal activator (El Ghaoui, *et al.* 2008) [28].
Urolithiasis preventive	70% Ethnaol/water extract prevented or reduced the formation of urinary tract stones (Ahmadi, *et al.* 2012) [29].
Cardiovacular protective*	Ethanolic extract of the flowers showed important preventive and curative effects of cariovasular disorders (Al-Snafi, 2013) [30]. * See remark to this property after this reference.
Hepatoprotective	70% Methanol/water extract of the plant found active against acetaminophen-induced hepatotoxicity in mice. The systematic work included three control groups (Hussain, *et al.* 2014) [31].
Hypoglycemic	Ethanolic extract showed hypoglycemic activity and three new compound were isolated and characterized (Zhang, *et al.* 2015) [32].
Latex allergy prevention	Hospital staff were treated with 8% aqueous extract where the test group washed their hands with it before and after use of latex gloves (Manesh, *et al.* 2015) [33].
Tyrosinase inhibition	A solution of 80% ethanol in water is effective at stopping the enzyme tyrosinase, which causes darkening of certain foods (Namjoyan, *et al.* 2015) [34].

Conclusions

Reviewing the scientific literature related to the genus Holyhock that was published over almost five decades, it is concluded that.

- The conventional applications of Hollyhock plants have been extensively recorded.

- Holyhock has a vast array of biological, medicinal, and other functions that span from using the plant or its components directly to nanochemistry.
- The chemical composition of Hibiscus rosa is not yet fully understood, even though it is the most studied. Further research is required to investigate its potential biological effects.
- The chemical compositions and biological activities of other subspecies of Holyhock are still not known, with only partial or very limited investigations conducted.
- Few subspecies of Holyhock were never studied for biological and other activities.
- Research on this genus is far from being finished.

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