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Review

Ursolic acid a promising candidate in the therapeutics of breast cancer: Current status and future implications

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ABSTRACT

Breast cancer [BC] is the deadliest neoplasm in women globally and the second leading cause of cancer associated deaths. Current treatment methods include chemotherapy, hormonal therapy, radiation therapy and surgery. However, BC has shown resistance to these therapies and are often associated with side effects, multidrug resistance, recurrence are the major issues in BC treatment. Currently, dietary phytocompounds have emerged as beneficial agents for the prevention and treatment of cancer because of their safe and cost effective nature. Ursolic acid [UA] is widely spread in fruits and vegetables having the ability to inhibit BC proliferation, angiogenesis and metastasis, arrest cell cycle, induced apoptosis, scavenge free radicals and regulate several anti-apoptotic and pro-apoptotic proteins. UA has also shown potential anticancer, anti-inflammatory and anti-oxidant activities in several human BC cells. This review paper encompasses the role of UA against BC and their mechanism of action *in vitro* and *in vivo* studies.

1. Breast cancer: a women dilemma

BC is an important public health problem worldwide responsible for ~30% new female cases and is ranked as the second cause of cancer associated deaths in annual statistics [1]. According to 2018 American Cancer Society statistical report the US alone will have ~1,735,350 new cases and 609,640 deaths, including 266,120 new cases of invasive BC [2]. BC not only occur in female but it also effect male and transgender [3].

Generally BC is divided into estrogen receptor positive [ER+] [T47D, MCF-7] and ER-negative [MDA-MBA-453, SKBR3, MDA-MB-231]. On the basis of several other molecular markers like human epidermal growth factor receptor [HER-2], progesterone receptor [PR], BC is further classified into different subtypes such as, luminal A [ER+ HER2-, PR+], luminal B [PR+, ER+, HER-2+], basal like and HER-2 positive one [4,5]. These different types of BC respond in a different way to different types of treatment strategies which make it more challenging to define accurate selection of chemotherapeutics or drugs that are both effective and safe to BC patients [5].

Large number of risk factors are related to BC like weight, age, gender, exogenous and endogenous hormone exposure, family history, lifestyle [diet, lactation, nulliparity, parity, early menarche, oral contraceptive use, tobacco, alcohol, diabetes, obesity, UV exposure, late night work [circadian disruption] [5,6]. Furthermore, mutations in genes such as BRCA1 and BRCA2 also account for 5–10% of different types of BC [5]. Some clinical features such as hormones, presence of metastasis, lymph node, histological grade, HER-2 receptor status are also routinely monitored to provide the patients' with the best possible therapy [7].

The highest rate of incidence of BC has been investigated in Asian countries because of poor BC health awareness, late detection systems, culture and religious hurdles, reluctance to visit male doctors, lack of screening and diagnosis centers [8,5]. BC is a devastating disease and it highly important to speed up its timely detection and diagnosis. The earlier we know about the status of cancer the less the problem will arise. Scientific community have designed several BC diagnosis tools

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such as ductogram, mammogram, MRI, ultrasound, breast self-examination, computerized tomography and biopsy, positron emission tomography *etc*. These diagnosis tools still have some limitations such as high cost, time consuming and not suitable for young females [9,5]. Therefore, scientists are trying to develop new diagnostic tools which are highly sensitive and timely detect BC stage. Currently, scientists have developed biosensors to detect BC using various biomarkers [gene and protein biomarkers] [10,11]. Apart from these scientists have developed micro wave imaging techniques [micro wave tomography], RF sensors, sensor array, radar based microwave imaging *etc* and are widely used as a promising screening tools for quick detection and diagnosis [5].

A wide range of BC therapies are available in the market such as chemotherapy [CT], radiation therapy [RT], hormones therapy [HT] and surgery [mastectomy, lumpectomy] [12,13]. However, these treatment strategies have some negative effects which has decreased their potential on BC cells [14]. One of the most threatening problem associated with cancer therapy is multidrug resistance [MDR], which is common cause of chemotherapy failure and recurrence due to which the survival rate of BC is very poor [15,5]. The survival rate of BC is different in different parts of the world ranging from 80% or above in developed countries [North America, Japan, Sweden *etc*], about 60% in developing countries and lower than 40% in under-developed countries [5]. It is the need of hour to develop more potential therapeutic approach with less/no side effects and more effectiveness. Therefore, phytocompounds have been proven as strong chemopreventive and chemotherapeutic strategy for BC treatment. Different epidemiological studies have proposed that high utilization of fruits and vegetables have significantly reduced the risk of BC by modulating different signaling pathways, scavenging ROS, inhibit angiogenesis and metastasis, stimulate caspases, induces apoptosis, arrest cell cycle which can give positive feedback and can play a key role in BC treatment [16,17]. UA is a potential phytocompound largely distributed in different fruits, vegetables and other dietary sources. UA is having promising anticancer, antioxidant, anti-inflammatory properties by regulating different signaling pathways, modulate the expression of different pro-apoptotic and antiapoptotic genes thereby developing BC treatment.

2. Chemistry, pharmacokinetics and health benefits of ursolic acid

One of the most abundant and most studied pentacyclic triterpene is 3-β-hydroxy-urs-12-en-28-oic acid, commonly named as UA with molecular structure $C_{30}H_{48}O_3$ and molecular mass 456.7 g/mol (Fig. 1). UA is found in large quantities in different fruits, vegetables, whole grains, dietary fibers, apples, pears, brown mustard star fruit, mahogany, daylily *etc* ranging from 0.15 to 1.8 g/100 g dry matter [18–20]. UA, a secondary plant metabolite is a terpene usually soluble in organic solvents but insoluble in water. Because of poor solubility and bioavailability UA has been administered as a liposome [21–23]. According to literature survey published, only three such studies have been performed only in Chinese [21–23].

UA has been investigated as a potential chemopreventive and chemotherapeutic agent against different types of BC. Interest in UA, as a health promoting agent has grown in recent years because of lower toxicity and potential antioxidant, anti-inflammatory and anticancer effects on normal and cancer cells [24–26]. There is also a very little evidence that suggest that UA enhances adverse metabolic reactions in *in vivo* when taken as part of regular diet. Furthermore, UA has been considerably known as chemopreventive agent in different *in vitro* and *in vivo* studies. Belding et al. [1998] in his research study investigated that UA was the main part of hydrocarbons [> 30%] in different apple varieties like Gala, Smith, Fuji and Granny Smith. Frighetto et al. [27] investigated that the normal UA concentration in the leaves was 0.8, 0.8, 0.5 and 0.2 mg/ cm^2 respectively. In addition, one other study has investigated that UA concentration in apple peels will not be as high as mentioned because of diverse solvents used for isolation and measurement [28]. Liao et al. [29] investigated that UA plasma concentrations has significantly increases to the threshold level at one hour after oral introduction in male rat and then gradually decreases [after 12 h]. But, the normal plasma concentrations was significantly low even after consuming high dose showing that UA either had poor bioavailability or having higher tendency to organ binding ability.

Moreover, UA has shown different organ binding and accumulation potential with the highest quantity in the lungs than spleen and hepatic cells. It is evident that UA accumulate in the body in a blood circulatory patterns. Some other *in vivo* studies revealed that kidney and liver were most suitable organs for UA accumulation [30]. There are certain limitations associated with UA such as bioavailability and specific target delivery. To enhance the bioavailability and specific targeted delivery scientists have developed some alternative strategies such as phospholipid nanoparticle to enhance the accumulation and distribution of UA in different organs [31]. UA has shown strong anti-BC potential through different cancer cell lines and animal models [Table 1]. Therefore, this article extensively examines the potential role of UA in chemoprevention and chemotherapeutics of BC.

2.1. Safety of ursolic acid

Research studies have clearly suggested that UA is non-toxic and might be utilized as a valuable therapeutic agent for the treatment of BC

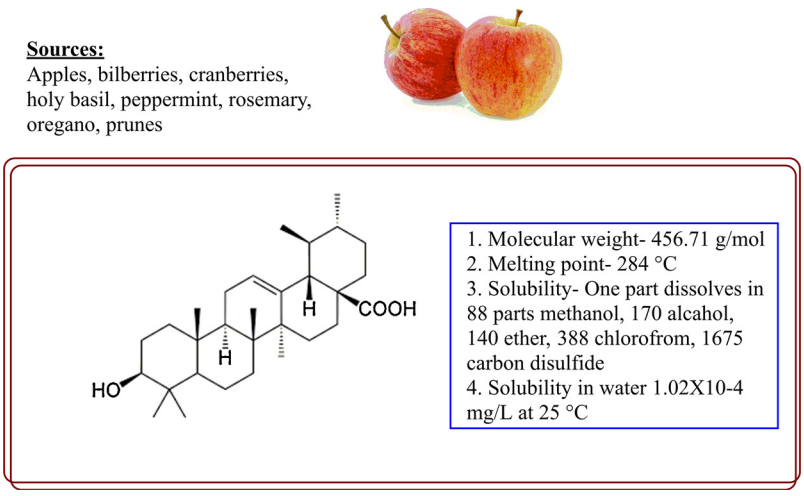

Fig. 1. Physical properties of chemical structure of ursolic acid.
Source: Apples, bilberries, cranberries, holy basil, peppermint, rosemary, oregano, prunes.