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Opinion Paper

The possible role of ursolic acid in Covid-19: A real game changer

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SUMMARY

Ursolic acid (UA) is a pentacyclic terpenoid is usually found in the fruit peels and stem bark as secondary metabolites. UA has antiviral, antibacterial, and antiparasitic properties. UA has a wide spectrum of pharmacological activities against different infections. Because of the greatest antiviral and anti-inflammatory properties of UA, so it could be a plausible therapeutic herbal medicine in Covid-19 treatment. Covid-19 is a recent worldwide virulent disease pandemic due to severe acute respiratory coronavirus disease 2 (SARS-CoV-2). The pathogenesis of SARS-CoV-2 infection is related to the direct cytopathic effect and exaggerated immune response by which acute lung injury (ALI) and/or acute respiratory distress syndrome might be developed in critical cases. UA may inhibit main protease of SARS-CoV-2, and inhibits the interface flanked by SARS-CoV-2 viral proteins and its entry point commonly recognized as angiotensin converting enzyme 2 (ACE2). In addition, UA attenuates SARS-CoV-2-induced inflammatory reactions and oxidative stress.

Therefore, UA could avert SARS-CoV-2 infection from causing ALI. This opinion proposed that UA might be a potential candidate therapy against Covid-19 and can mitigate post-Covid-19 complications such as lung fibrosis. In this regards, forthcoming studies are reasonable to substantiate the therapeutic role of UA in Covid-19. However, taken into account that Covid-19 is yet to be investigating for further evaluations, therefore, clinical trials are recommended regarding use and dose of UA in Covid-19 treatment, as well as secondary effects.

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1. Background

Ursolic acid (UA) is a pentacyclic terpenoid with unique chemical structure (Fig. 1). UA is usually found in the fruit peels and stem bark as a secondary metabolites [1]. UA is used as a herb extract in the folk medicine for centuries as it found in leaves of rosemary, thyme, oregano, lavender, and hawthorn. UA is mainly used in the treatment and prevention of cancer through attenuation of proliferation and metastasis via modulation of metabolic pathways [2].

Moreover, UA has been identified to be an important nutritional remedy prevents muscle atrophy, enhances glucose tolerance, and reduces hyperlipidemia-induced hepatic steatosis [3]. UA has antiviral, antibacterial, and antiparasitic properties, so it has a wide spectrum of pharmacological activities against different infections.

As well, UA possesses anti-inflammatory and immune-modulating effects reducing inflammatory reactions in different immunological and autoimmune disorders [4].

The usual dose of UA that recommended in the treatment of various disorders is 300 mg/day. UA is usually used to increase muscle mass in athletics and reduce body weight mainly waist circumference and body mass index in obese subjects [41]. Moreover, UA is effective for treatment of different cardiovascular complications including heart failure, hypertension, and tachycardia by cardioprotective effects [7]. UA restore enzyme activity and prevents DNA damage of cardiomyocytes [7]. UA improves peripheral insulin sensitivity, inhibits development of insulin resistance with regulation of insulin secretion from pancreatic β -cells [16]. Therefore, UA is efficient in attenuation of diabetic nephropathy through mitigation of hyperglycemia-induced oxidative stress and inflammatory reaction in the kidneys [13]. In addition, UA has imperative action on the bone; it reduces the activity of osteoclasts and improves osteoblastic activity, thereby reducing risk for development of osteoporosis [42]. Despite of these potential

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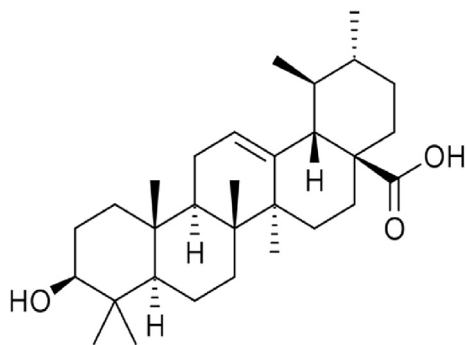


Fig. 1. Chemical structure of ursolic acid.

benefits from use of UA, it may have some adverse effects including nausea, vomiting, abdominal pain, mild hematuria, skin rash and hypernatremia [45]. The most dangerous adverse effects from using of UA are dose-dependent hepatotoxicity [46] and promote vascular plaque formation and may increase risk of cardiovascular complications [47]. However, UA should not be an alternative for approved medical remedies. The most important pharmacological effects of UA on the clinic-pathological disorders are revised and summarized [Table 1].

2. Mechanism of action of ursolic acid

The main mechanism of UA is related to the different pathways, one key mechanism is the ability of UA to inhibit mitogen activated protein kinase (MAPK) and mammalian target of rapamycin (mTOR), which involved in cell replications, and growths as well as different inflammatory pathways [43]. Besides, UA blocks cyclooxygenase-2 (COX-2) enzyme, which is important for development of inflammation [39] and nuclear factor kappa B (NF- κ B), a signaling pathway vital in the regulation of immune response [34]. Likewise, UA attenuates oxidative stress through inhibition generation of reactive oxygen species (ROS) and potentiating of endogenous antioxidant capacity [44].

UA has important drug interaction effects, it inhibits organic anion transporter polypeptide 1 B1 (OATP1B1), which is important for transport of drugs like statins, valsartan, enalapril and bosentan from portal circulation into the liver to be metabolized [48]. In addition, UA blocks glucuronosyltransferase activity (UGT1A4), which is necessary for metabolism of lamotrigine [49].

3. Antiviral effects of ursolic acid

UA blocks human immune deficiency virus (HIV-1) protease, an essential aspartyl enzyme for synthesis of mature protein and

polypeptide components of HIV-1 virion [18]. UA is also efficient against chronic hepatitis C (HCV) through inhibition of NS5B RNA-dependent polymerase and can be used alone or in combination with other anti-HCV drugs [19]. Furthermore, UA has anti-herpes activity by blocking early stages of herpes simplex virus adsorption and replication [20]. Tohme et al., confirmed that UA interferes with rotavirus replication cycle via suppression synthesis of VP6 and NSP2 viral proteins so; can be used as a new therapy against rotavirus infection [21]. Moreover, UA is a powerful and selective inhibitor of papilloma virus mainly human papilloma virus type 11 without cytotoxicity [22]. Song et al., observed that UA is powerful inhibitor of influenza virus (H5N1) entry [23]. Additionally, UA limits proliferation and spreads of enterovirus 71 (EV71) [24]. In vitro study revealed that UA reduces expression of human papilloma virus –18 (HPV-18) E6/E7 genes in HeLa cells; however expression of p53 did not change [25]. Similarly, a recent study by Chen et al., revealed that UA derivatives are effective against porcine reproductive and respiratory syndrome virus through direct inactivation of viral virion and replication [26].

From these findings, UA has broad-spectrum anti-viral activities, by which it reduces viral load and viral proliferation through interruption of viral replication cycle [27].

4. SARS-CoV-2 infection and ursolic acid

Because of the greatest antiviral and anti-inflammatory properties of UA, so it might be a plausible therapeutic herbal medicine in treating Covid-19, a recent worldwide virulent disease pandemic due to severe acute respiratory coronavirus disease 2 (SARS-CoV-2) [28]. The pathogenesis of SARS-CoV-2 infection is related to the direct cytopathic effect and exaggerated immune response by which acute lung injury (ALI) and/or acute respiratory distress syndrome might be developed in the critical cases [28]. Contemporary *in silico* and docking studies observed that UA may inhibit main protease of SARS-CoV-2 [29]. Subbaiyan et al., showed that UA also inhibits the interface flanked by SARS-CoV-2 viral proteins and its entry point commonly recognized as angiotensin converting enzyme 2 (ACE2) [30]. Thus, the anti-SARS-CoV-2 activity of UA increases the probability for using of UA in the treatment of Covid-19. Though, updated *in vitro* and *ex-vivo* experimental studies are recommended to determine the precise mechanism of anti-SARS-CoV-2 activity of UA.

In severe critical infections, overstated immune response and elevated pro-inflammatory cytokine level are linked with progression of ALI and/or ARDS [31]. Yang et al., experimental study in mice found that UA attenuates development of heat stress-induced-ALI [31]. This pulmoprotective effect of UA is might be through suppression release of inflammatory and pro-inflammatory cytokines mediated by activation of p38 mitogen-

Table 1
The Pharmacological effects of Ursolic Acid.

The clinical-pathological findings	References
UA is a weak aromatase inhibitor may be used for infertility	Gnoatta et al. [5].
UA effective against obesity by decreasing white fat and increasing brown fat	Kunkel et al. [6].
Cardioprotective through anti-oxidant effect	Liobikas et al. [7].
Effective for treatment of multiple sclerosis by inhibiting Th17	Zhang et al. [8].
Inhibits inflammation-induced cognitive dysfunction	Wang et al. [9].
Effective in the management of prostatic cancer	Meng et al. [10].
UA has anti-fibrotic effect through inhibition of NADPH oxidase	Hel et al. [11].
UA has anti-cancer effects through inhibition of signaling pathways	Lin et al. [12].
UA is effective for diabetic nephropathy	Ling et al. [13].
UA is effective for management of inflammatory bowel disease	Chun et al. [14].
UA is effective for management of inflammatory arthritis	Baek et al. [15].
UA has anti-diabetic effect by enhancing of insulin secretion and attenuation of insulin resistance	Castro et al. [16].
UA has significant antibacterial activity	Zhou et al. [17].

activated protein kinase (p38MAPK) [32]. Therefore, UA could avert SARS-CoV-2 infection from causing ALI through modulation of pro-inflammatory and inflammatory signaling pathways.

Interestingly, extravagant hypercytokinemia, which linked with development of cytokine storm in Covid-19, is mainly mediated through direct activation of p38MAPK and nuclear factor kappa B (NF-κB) [33]. It has been reported that UA can prevent the development of inflammation and oxidative stress by inhibiting of p38MAPK and NF-κB signaling pathways [34]. Likewise, UA could prevent activation of NLRP3 inflammasome during acute inflammatory reactions [34], thus it may reduce risk for development of cytokine storm mediated by NLRP3 inflammasome stimulation by SARS-CoV-2 [33]. Therefore, suppression of p38MAPK, NF-κB and NLRP3 inflammasome signaling pathways by UA might be a protective mechanism against exaggerated immune-induced ALI in Covid-19.

Extraordinarily, renin-angiotensin aldosterone system (RAAS) is extremely dysregulated during SARS-CoV-2 infection, characterized by elevation of angiotensin II (AngII) due to down-regulation of ACE2. AngII through angiotensin receptor type 1 (ATR1) induce the release of pro-inflammatory cytokines, activation of inflammatory signaling pathways, triggering of procoagulant cascades and development of ALI [35]. Ma et al., illustrated that UA may attenuate progress of inflammation, oxidative stress, and release of pro-inflammatory cytokines through down-regulation of AngII/AT1R signaling [36]. In this sense, controlling of AngII/AT1R signaling dysregulation during acute SARS-CoV-2 by the effect of UA could propose that UA may temper AngII-mediated ALI/ARDS.

Besides, UA may hamper the development of lung fibrosis through inhibition the activity and release of transforming growth factor beta (TGF-β) [37], which is over-activated in Covid-19 and linked with post-Covid-19 lung fibrosis and other life-threatening sequelae [38]. So, prolong use of UA mainly in patients with severe Covid-19 may reduce risk for development of post-Covid-19 complications like lung fibrosis.

Also, UA inhibits the activity of COX-2 enzyme, which engaged with cell proliferation and malignant transformation [39]. COX-2 is triggered during SARS-CoV-2 infection, leading to lung inflammation and augmentation of fibro-proliferative response to the SARS-CoV-2-induced ALI [40]. Hence, UA may have a potential effect in the management of severe Covid-19 by inhibiting COX-2-induced lung inflammation.

The net-final effect of UA in SARS-CoV-2 infection is mediated through direct anti-SARS-CoV-2, anti-inflammatory effects, suppression of inflammatory signaling pathways inhibition and release of pro-inflammatory cytokines [Fig. 2].

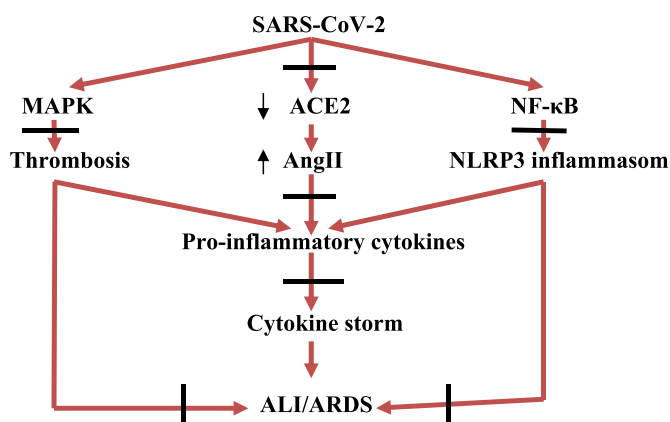


Fig. 2. The potential role of ursolic acid in the SARS-CoV-2 infection: (⊥) The inhibitory effect of ursolic acid.

5. Conclusion

These findings proposed that UA might be a potential candidate therapy against Covid-19 and can mitigate post-Covid-19 complications such as lung fibrosis. In this regards, forthcoming studies are reasonable to substantiate the therapeutic role of UA in Covid-19. However, taken into account that Covid-19 is yet to be investigating for further evaluations, therefore, clinical trials are recommended regarding use and dose of UA in Covid-19 treatment, as well as secondary effects. At present time, no recommendation can be made about UA, doses and time of use. Repurposing of approved anti-inflammatory drugs and investigate their efficacy against inflammatory signaling pathways, which are targeted by UA might of value in Covid-19 treatment.

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Authorship

HMK performed study design and writing AIA performed critical review and preparation of the manuscripts. Both authors revised and approved the final proof.

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Declaration of competing interest

The authors had no conflicts of interest to declare.

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