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Ginsenosides: An overview of its antiplatelet effects and its underlying mechanisms

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ABSTRACT: Ginsenosides, the principal constituent of plants from genus *Panax*, have been indicated in multitudinous of ailments by the *Homos sapiens*, for more than 2 millennia. Mostly and notably the ginsenosides, the mainstay of Chinese herbal system of medication, are harnessed for multifarious disorders viz. Neurodegenerative diseases, Diabetes mellitus, Cardiovascular abnormalities, Septic shock, inflammatory disorders, Obesity and most striking of all owing to the prevalent circumstances have to potential to manage, even treat COVID-19, albeit empirically. Whereas, considering the plant itself, it strikes to the researcher as perennial although, with significantly slow progress. The spectrum of the review encompasses the functional reach of the ginsenosides with special emphasis on the antiplatelet therapeutics, in conjunction with the notoriety and the prospect of the compounds in multitude of disorders. However, the mechanism on which the edifice, of the antithrombotic efficiency is contingent, is expressed with keen interest. Ultimately, the root or its extract, is evidenced to be sufficiently effective in curbing the foresaid ailments whether authenticated by systematic review, clinical trials, mechanistic patterns and animal investigations. Overall, the herb shows immense potential to be packaged into a unit dosage form and be brought in the prevalent market especially as an antithrombotic agent.

Keywords: Ginsenosides, Antiplatelet effects, antiplatelets Mechanism.

1. Introduction

Over 2000 years have passed since the first use of ginseng which, alibeit classified into Panax genus, finds it utility in nourishment and medicine. In folklore it is called Rénshēn, Insam and Ninjin in Chinese, Korean and Japanese, respectively. There are numerous species in the Panax genus, amongst which, American (Panax quinquefolius L., Meyer) in addition to Asian (Panax ginseng C.A. Meyer) and being the most renounced of them all notwithstanding the fact that they are distinct in bioactivities and chemical composition. Asian ginseng has numerous bioactive compounds viz. saponins, poly-phenols, polyacetylene, alkaloids, unbound amino acids and polysaccharides are among the chemical substances. Its multifaceted qualities have long been acknowledged, including but not

limited to antineoplastic, Antiangiogenesis, antiemetic, antimetastatic, proapoptic, antioxidative and anticoagulative properties. In perspective of individualistic species, the Asian ginseng bears, in tangible amounts of phenolics and Ginsenosides, responsible for its most

The Acanthopanax family comprises of but not limited to the perennial herb Panax ginseng Meyer. It is a priceless restorative medication that has historically been manufactured mostly in Japan, korea, Northeast China and eastern Russia. Evidence on ginseng has grown recently, both domestically and internationally. Ginseng has a strong medical significance and a range of pharmacological effects since it has historically been thought of as an all-encompassing "cure all". There are 150 different types of ginsenosides at this time, which may be classified into two groups: the tetracyclic triterpenoid dammarane type being the first and the pentacyclic triterpenoid oleanolane type being the second [22]. Myriad types of ginsenosides are prevalent that can perform a variety of therapeutic tasks and exhibit markedly distinct biological activities. Recent research has demonstrated that ginsenosides can have therapeutic indication to treat cardiovascular disease through a particular mechanism. Ginsenosides have a strong defense against cardiovascular disease, especially when it comes to vascular remodeling, proliferation, and the creation and durability of atherosclerotic plaque. Since it controls the cycle of cell proliferation, gene pathways associated with inflammation, cytokines, lipid metabolism as well as myriad of other biochemical processes to prevent the onset relating to the atherosclerotic disease, it can be utilized in management of Atherosclerotic plaque (Xue et al., 2021). Many therapeutic advantages have been attributed to the components of ginseng including but not limited to ginsenosides. The efficacy of the ginsenosides can be implicated in the degradation and degeneration of neurons and axons thereto, in the central nervous system resulting in neurodegenerative diseases like Parkinson's disorder (PD), Alzheimer's disease (AD), Huntington's disease, multiple sclerosis (MS), , amyotrophic lateral sclerosis (ALS), and cerebral ischemia, which can impair cognition, behavior, and motor function (Rajabian et al., .

consequential biological benefits. To date more than 25 ginsenosides classes and circa more than 10 phenolics named gentistic. Ferulic, cinnamic, p-hydroxybenzioc and syringic acids have been identified owing to myriad of methods and cultivating conditions (Chung et al., 2012).
2019). Furthermore, ginsenosides have been evidence in ameliorating conditions viz. sexual dysfunction, Metabolic disorders the likes of Diabetes, Nonalcoholic fatty liver disease, Hyperlipidemia and Obesity, cardiovascular diseases (CVD), Neoplastic disorders, Respiratory ailments, Ulcers and antimicrobial diseases (Jeong et al., 2014; Kim et al., 2013; Lee and Kim, 2014; Sun, 2011).

1.1 Chemical Constituents

Ginsenosides can be classified as tricyclic triterpenoids of the dammarane type or the oleanene type based on their structural characteristics. Depending on whether a C6-OH is located on the C-3, C-6, C-12, or C-20 of the skeleton, the dammarane type can be separated into protopanaxadiol (PPD) and protopanaxatriol (PPT). Furthermore, depending on where the chiral carbon substitution is located in protopanaxadiol and protopanaxatriol, the C-20 is separated into 20(S) and 20(R)-type structures. Ginsenosides are further classified based on the presence or absence of hydroxyl groups at 6 positions of the chemical structure, with the six positions without the hydroxyl group. In contrast to PPT, which mostly consists of the ginsenosides Re, G1, Rg2, and Rh1, PPD primarily consists of the ginsenosides Rb1, Rb2, Rb3, Rc, Rd, Rg3, and compound K. Ginsenoside Ro is the most prevalent example of the oleanolane-type ginsenosides and was once thought to be the oleanolic acid-c type. Currently, 70 triterpenoid saponins from ginseng have been extracted and identified. According to the skeleton's structure, the ginsenosides we chose for this study that have anti-diabetic actions fall into the following groups (**Figures 1, 2**) (Bai et al., 2018; Wang et al., 2021). However, the most comprehensive classification for the ginsenosides has been illustrated by Hou M et al. (2020) and is pictorially depicted in **Fig 3** and **3a**.

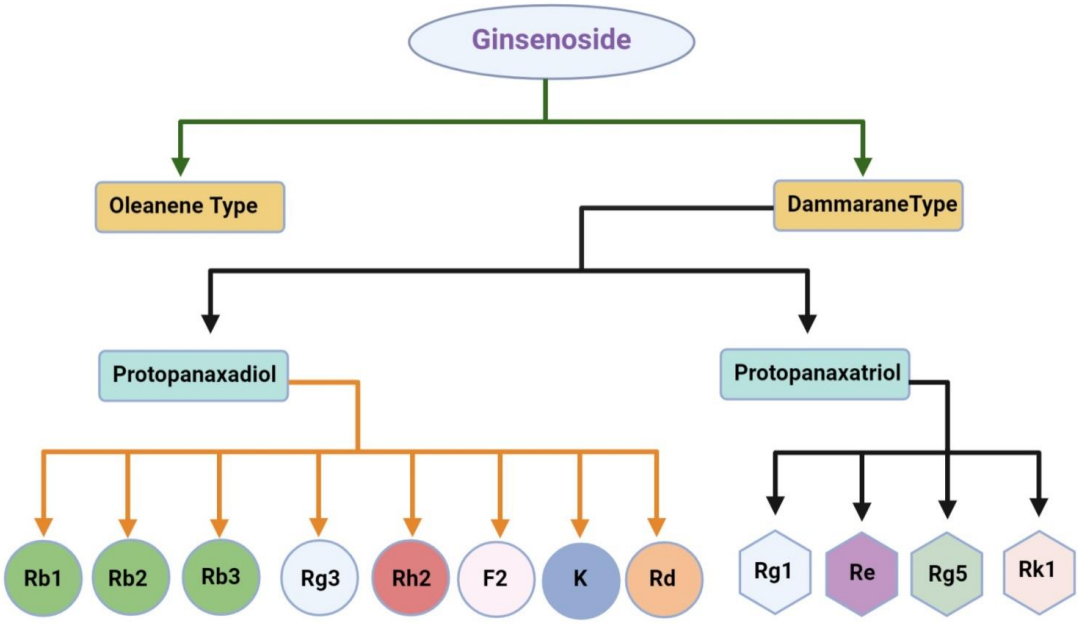


Figure 1: Crude classification of Ginsenosides

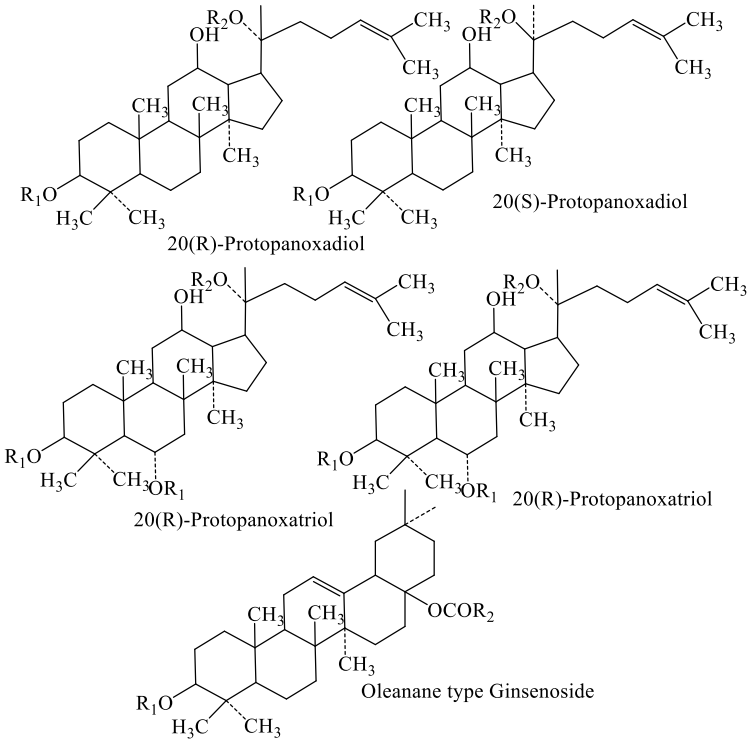
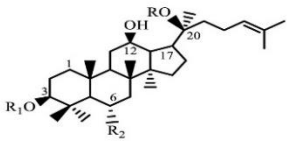


Figure 2. The Protopanaxadiol (PPD), Protopanaxadiol (PPT) and the Oleanane type skeletons along with the Racemic forms (where applicable) (Bai et al., 2018).

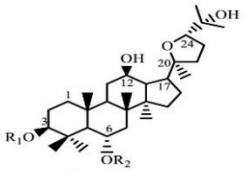
A



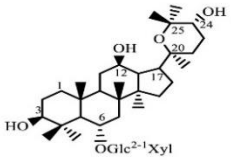
PPD or PPT-type

Compd. (PPD/PPT)	R (H)	R_1 (H)	R_2 (H/OH)
Ginsenoside Rb1	Glc^1-^{6}Glc-	Glc^1-^{2}Glc-	H
Ginsenoside Rb2	$Arap^1$-^{6}Glc-	Glc^1-^{2}Glc-	H
Ginsenoside Rb3	Xyl^1-^{6}Glc-	Glc^1-^{2}Glc-	H
Ginsenoside Rc	$Araf^1$-^{6}Glc-	Glc^1-^{2}Glc-	H
Ginsenoside Rd	Glc-	Glc^1-^{2}Glc-	H
Notoginsenoside Fc	Xyl^1-^{6}Glc-	Xyl^1-^{2}Glc^1-^{2}Glc-	H
Chikusetsusaponin III	H	Xyl^1-^{6}Glc^2-^{1}Glc	H
Ginsenoside Rh2*	H	Glc-	H
Ginsenoside Rg3*	H	Glc^1-^{2}Glc-	H
Ginsenoside CK*	Glc-	H	H
Malonyl-Rb1	Glc^1-^{6}Glc-	Malonyl-^{6}Glc^1-^{2}Glc-	H
Malonyl-Rb2	$Arap^1$-^{6}Glc-	Malonyl-^{6}Glc^1-^{2}Glc-	H
Malonyl-Rc	$Araf^1$-^{6}Glc-	Malonyl-^{6}Glc^1-^{2}Glc-	H
Malonyl-Rd	Glc-	Malonyl-^{6}Glc^1-^{2}Glc-	H
Malonyl-Re	Malony1-^{6}Glc-	H	Rha^1-^{2}GlcO-
Ginsenoside Re	Glc-	H	Rha^1-^{2}GlcO-
Ginsenoside Rf	H	H	Glc^1-^{2}GlcO-
Ginsenoside Rg1	Glc-	H	GlcO-
Ginsenoside Rg2	H	H	Rha^1-^{2}GlcO-
Notoginsenoside R1	Glc-	H	Xyl^1-^{2}GlcO-
Notoginsenoside R2	H	H	Xyl^1-^{2}GlcO-
Ginsenoside F1*	Glc-	H	HO-
Ginsenoside Rh1*	H	H	GlcO-

B



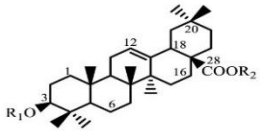
Ocotillo-type



Vinaginsenoside R11

Compd. (Ocotillo)	R_1 (H)	R_2 (H)
Pseudoginsenoside RT5	H	Glc-
Pseudoginsenoside F11	H	Rha^1-^{2}Glc-
Majonoside R1	H	Glc^1-^{2}Glc-
Majonoside R2	H	Xyl^1-^{2}Glc-
Vinaginsenoside R1	H	Rha^1-^{2}Glc^6 (Ac)-
Vinaginsenoside R2	H	Xyl^1-^{2}Glc^6 (Ac)-

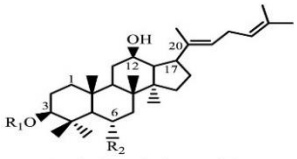
C



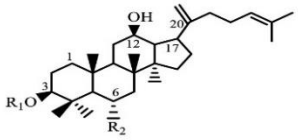
Oleanane-type

Compd. (Oleanic acid)	R_1 (H)	R_2 (H)
Chikusetsusaponin IVa	GluA-	Glc-
Ginsenoside Ro	Glc^1-^{2}GluA-	Glc-
Chikusetsusaponin IV	$Araf^1$-^{4}GluA-	Glc-
Stipuleanoside R1	$Araf^1$-^{4}$GluA^3$-^{1}Glc	H
Stipuleanoside R2	$Araf^1$-^{4}$GluA^3$-^{1}Glc	Glc-
Zingibroside R1	Glc^1-^{2}GluA-	H
Pseudoginsenoside RT1	Xyl^1-^{2}GluA-	Glc-

D



Dehydrated ginsenoside



Dehydrated ginsenoside

Compd.	R_1	R_2	Compd.	R_1	R_2
Ginsenoside Rh3*	Glc-	H	Ginsenoside Rk1*	Glc^1-^{2}Glc-	H
Ginsenoside Rh4*	H	GlcO-	Ginsenoside Rk2*	Glc-	H
Ginsenoside Rg5*	Glc^1-^{2}Glc-	H	Ginsenoside Rk3*	H	GlcO-

Figure 3: Represents and elicits the classification of ginsenosides. Wherein, (A) structurally, PPT or the PPD class of ginsenosides, to start. (B) Ginsenosides of the ocotillo class (C) Ginsenosides of the oléanane chemical group. Dehydrated ginsenosides are (D). Asterisks denote ginsenoside intermediates (hot chemicals). The branching glycosides chikusetsusaponin III, stipuleanosides R1 and R2, and sapogenins' connections to Glc or GluA's C-1 (marked by red) (Hou et al., 2021).

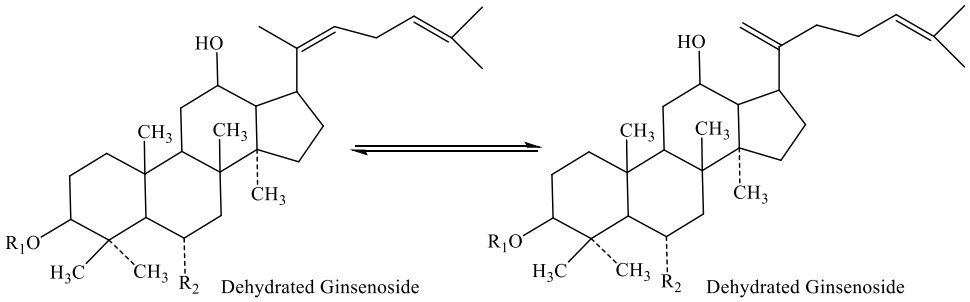


Figure 3a: Likewise, above investigators also hinted upon the equilibration among the two dehydrated forms of a quintessential Ginsenoside wherein, the double bond at position 20 oscillates about thereby, resulting in different conformations and subsequent stabilization of Pi electronic density.

2. Therapeutics potential of antiplatelet effect

2.1. Sepsis

One of the most likely causes for intensive care unit (ICU) admission is sepsis, which can result in multiple organ failure and mortality (Eisen et al., 2012; Lobo et al., 2011; Martin et al., 2003). Sepsis is steadily becoming more common globally, with millions getting sick each year. Sepsis patients have a 25% mortality rate (Angus et al., 2001; Dellinger, 2003) and the cost of sepsis therapy in the US is over $17 million a year (Angus et al., 2001). Studies have demonstrated that unchecked inflammatory responses and pro-coagulant effects play a significant role in the onset of sepsis, and that coagulation system problems can manifest in disseminated intravascular coagulation and subsequently the intravascular microthrombus production. The production of microthrombi and the release of inflammatory factors in this sequence of events are significantly influenced by platelet-endothelial cell contacts and platelet-neutrophil interconnections caused by platelet activation (Li et al., 2015; Wang et al., 2018; Wiewel et al., 2016). As a result, using antiplatelet medications to reduce platelet activity in sepsis patients may result in more favorable outcomes.

Contradictory findings emerged from study on the impact of antiplatelet medications on the prognosis of sepsis patients, though. The mortality rate (Falcone et al., 2015; Osthoff et al., 2016) in patients with sepsis or infectious disorders as well as those who are severely sick (Sossdorf et al., 2013) has been demonstrated in certain trials to be decreased by antiplatelet medications by lowering platelet activity and decreasing platelet aggregation (O'Neal Jr et al., 2011; Thomas et al., 2015). Animal studies have provided additional evidence that antiplatelet medications are beneficial for sepsis patients (Eisen, 2012; Ulu et al., 2015). Other research, however, has demonstrated that the administration of antiplatelet medications has little impact on sepsis patients or those who are detrimentally unwell (Chen et al., 2015; Erlich et al., 2011). Antiplatelet therapy's impact on sepsis is thus still unknown. Aspirin boosts the likelihood of survival in pertinence to mice and dogs in animal models of antiplatelet treatment for sepsis via decreasing platelet thromboxane A2 production (Eisen et al., 2021; Halushka et al., 1981; Hinshaw et al., 1967). Whereas, Clopidogrel did not substantially increase survival and hemodynamics in the first 24-48 h of a research utilizing P2Y12 inhibitors in mice, although it tended to lower mortality in the latter time frame in the experimental group (Winning et al., 2009). The experimental group in a study on GPIIb/IIIa antagonists using a septic shock rabbit model died less frequently than the control group. According to the notion, GPIIb/IIIa antagonists prevent endothelial dysfunction by inhibiting platelet aggregation, monocyte tissue factor expression, and coagulation activation (Pu et al., 2001).

However, the pathway was not as rosy and susceptible to fair share of setbacks in respect of mortality. Tsai et al. (2015) reports circa 683421 patients of total suffering sepsis admitted in the hospital and among which 117447 were subjected to oral antiplatelet agent the likes of clopidogrel, aspirin and ticlopidine resulting in mortality (Tsai et al., 2015). Similarly, Campbell et al (2015) oversaw patients administered aspirin prior to ICU admission pertaining sepsis wherein 12 of 218 culminated in mortality (Campbell et al., 2015). In another analysis weiwel et al. (2016) tackled patients admitted in respect of sepsis, in addition, to pre-existing antiplatelet therapy and administered prasugrel, clopidogrel, dipyridamole and aspirin yet 267 of total 972 died (Wiewel et al., 2016). Harbi et al (2016) noted the same fate for 47 of 194 patients treated with aspirin this time however, as a continuation of preexisting regimen. Two years later Hsu et al. supervised 1526 patients on aspirin leading to organ failure and eventually death (Al Harbi et al., 2016; Ouyang et al., 2019)

2.2. COVID – 19

Anticoagulants may provide patients with COVID-19 a number of possible advantages, including a decreased risk of thrombotic illness as well as some anti-inflammatory effects against sepsis and curb the onset of acute respiratory distress syndrome. Heparins suppress neutrophil response, block P-selectin, platelet and neutrophil cross-talk, and decrease the production of IL-1, IL-6, E-selectin, and intercellular adhesion molecule 1 (Godino et al., 2021). Spaetgens B et al. (2022) denominates the efficacy of antiplatelet therapy in the COVID 19 mortality as debatable and requiring further investigation (Spaetgens et al., 2022). APT (antiplatelet treatment), according to Sontaro F et

al. (2021), was linked to decreased in-hospital mortality. Patients on other APT medications, such as clopidogrel, ticlopidine, ticagrelor, and prasugrel, in addition to aspirin, were also included in this research. Of the 50 patients who got DAPT (Double antiplatelet treatment), 29 were admitted in lieu of acute coronary syndrome, with the remnant patients receiving the contrary. Patients in the current research who received APT were a subgroup of more serious patients with a greater frequency of diabetes amongst the male sex. It's interesting that APT treatment was linked to a reduction in the time needed for mechanical ventilation (Santoro et al., 2022).

There may have been a slight caveat in respect of using the oral anticoagulant as found out by the Chow JH et al (2021) wherein, they administered anticoagulant prior to hospital admission. Patients receiving pre-hospital antiplatelet medication had a substantially decreased in-hospital mortality rate (18.9% vs. 21.5%, p .001), which translated into a 2.6% absolute mortality reduction (HR: 0.81, 95% CI: 0.76-0.87, p .005). To avoid one hospital mortality, on average, 39 people had to be treated. The risk of pulmonary embolism was substantially reduced (2.2% vs. 3.0%, p =.002) while the rate of epistaxis was significantly greater (0.9% vs. 0.4%, p .001) in the antiplatelet treatment group. The incidence of further hemorrhagic or thrombotic consequences did not differ in significance (Chow et al., 2021). Zhou et al (2020) tends to demystify the enigma in clearing up the field in what they affirm that the pre-hospital aspirin usage was linked to a decreased probability of expiry and severe acute respiratory distress syndrome (ARDS) in individuals with community-acquired pneumonia. Choice of P2Y12 also holds significant premise wherein, in spite of the fact that all oral P2Y12 inhibitors decrease platelet-leukocyte aggregates and platelet-derived pro-inflammatory cytokines from -granules, ticagrelor is exceptional in that it has the only well-documented ancillary target of inhibition viz, the equilibrative nucleoside transporter 1 (ENT1), which contributes to inhibition of cellular adenosine uptake. As a result, ticagrelor has stronger anti-inflammatory effects by simultaneously inhibiting the ENT1 and platelet P2Y12 receptors. Fortunately, the XANTHIPPE (Targeting Platelet-Leukocyte Aggregates in Pneumonia With Ticagrelor) trial, post-hoc analyses of the PLATO study (NCT00391872), and basic researches provide compelling evidence establishing the therapeutic significance of ticagrelor in the management of pneumonia by reducing lung injury and sepsis complications (Zhou, X. et al., 2020).

2.3. Cancer

Studies are indicative pertaining to precipitation of thromboembolic events by the selective estrogen receptor modulators. Leite et al. (2018) put forwards an argument in favour of proficiency of aspirin as an adjunctive therapy. In a systemic review and meta-analysis they contend that aspirin medication offers possible breast cancer risk reduction along with protection against cardiovascular events, and that additional research is necessary to assess the advantages of the drug's combination with endocrine therapy (Leite et al., 2018). Antiplatelet medications also have anticancer properties. Cyclooxygenase (COX)-2, which stimulates inflammation and cell growth, is inhibited by aspirin (Brown and DuBois, 2005). Apoptosis induction, NF-B inhibition, and polyamine catabolism are a few more pathways that have been studied (Schwenger et al., 1997). Patients with colorectal cancer, breast cancer, and lung cancer had lower mortality and recurrence rates while taking aspirin (Zhou et al., 2019). In contrast to aspirin, clopidogrel works by inhibiting the P2Y12 adenosine diphosphate receptor (Rodríguez-Miguel et al., 2019). Tumor metastasis was inhibited by blocking platelet activity via a P2Y12-dependent mechanism (Mezouar et al., 2015). In actuality, clopidogrel decreased the likelihood that prostate cancer and colon cancer would metastasize. After doing a statistical study, Hayashi T (2020) arrived to the conclusion that, following HCC treatment, antiplatelet therapy protected liver function and stopped tumour development. Therefore, antiplatelet therapy reduced liver-related fatality in HCC patients (Hayashi et al., 2020). A study by Ohia H et al. (2020) denominated an interesting finding for a clinical setting relating patients with colorectal cancer. According to the study, there were no appreciable differences between colorectal cancer patients who received laparoscopic resection while maintaining antiplatelet treatment in the lead-up to surgery and those who did not, in terms of the surgical results or postoperative problems. It may be preferable for patients undergoing laparoscopic surgery for colorectal cancer to keep receiving antiplatelet treatment from the perspective of

cardiovascular and cerebrovascular risk (Ohya et al., 2021).

3. Medicinal uses of Ginsenosides: an overview

Multifarious uses of Ginsenosides from ginseng species ranging from cancer to Alzheimer's. Herein, we endeavor to explore a few of them in lieu of the manuscript.

3.1. Cerebral disorders

Rg1 refurbish neural damage brought on by brain injury and contains anti-inflammatory and antioxidant properties. Our lab is primarily concerned with the development of ginseng's pharmacology in AD (Alzheimer disease). Rg1 is a triterpenoid saponin and one of ginseng's main bioactive components (Tang et al., 2017). Glucocorticoid receptor (GR) expression was considerably reduced in the dexamethasone therapy group. The expression of GR was considerably elevated by RU486 and Rg1 administration (2 and 4 mg/kg) compared to the dexamethasone treatment group (Zhang et al., 2017). Rg1 prevents behavioural flaws and slows down neuronal ageing. By curtailing NOD-like receptor protein 1 (NLRP1) inflammasome activation, Rg1 suppresses the effects of neuroinflammatory damage (Yi, 2019). In the hippocampus of mice that received GR injections, Rg1 impeded the activation of NLRP1 inflammasome elements and inflammasome-specific proinflammatory cytokines (Zhang et al., 2017). Rg1 was discovered to have an inhibitory impact on inflammasome activation in a recent analyses that looked at the development and progression of AD in animal models. In the frontal cortex and CA1 regions, it was demonstrated that Rg1 reduces ROS production and mitigates neuronal oxidative stress (Wang et al., 2014). The mechanisms underpinning the action of Rg1 on glucocorticoid-induced neuronal damage include the suppression of NLRP1 inflammasomes (Zhang et al., 2017).

Rg1 also plays a substantial part in various brain illnesses, despite the fact that the underlying processes are not precisely the same. Rg1 significantly reduces depression-like behaviour in rats in a depression paradigm, safeguards astrocyte gap junctions in the prefrontal cortex, and demonstrates antidepressant-like effects. Model rodents' behaviour alterations are prevented, levels of corticosterone (CORT) and corticotropin releasing hormone are decreased (Zhou et al., 2015), and rats' cerebral and cerebellar damage from obstructive jaundice is prevented by inducing TIPE-2 (Wang et al., 2015). Rg1 reduces the hypothalamic-pituitary-adrenal axis's dysregulation in the rat model of neuroinflammation-induced behavioural impairments and specifically numbs the rise in circulating IL-6 (Zheng et al., 2014).

By controlling the production of apoptotic signal proteins, lowering ROS, and preventing NSCs from becoming phosphorylated at the p38/JNK2 site, Rg1 shields neural stem cells (NSCs) in a stroke model from oxygen glucose deprivation-induced cell death (Li et al., 2017). Rg1 has neuroprotective benefits in a Parkinson's disease (PD) model both in laboratory and animal analyses, primarily through controlling the Wnt/-catenin signalling mechanism (Zhou et al., 2016). It lowers blood levels of pro-inflammatory cytokines, protects TH+ cells in the cerebral premise of substantia nigra pars compacta, from over accumulation, and inhibits microglia activation (Zhou et al., 2015). Moreover, the outcomes demonstrated that in both SPS and LPS in-vivo models, ginsenoside G-Rg1 promoted fear eradication and inhibited depressive-like behaviours. The expression of pro-inflammatory cytokines (CKs) including but not limited TNF-α and IL-1, the sensitization of microglia and astrocytes, and alleviation of synaptic proteins pertinent to the hippocampus, were all significantly ameliorated by ginsenoside Rg1 (Arc, PSD95, and GluA1). Additionally, Rg1 decreased the rise in Kir4.1 and GluN2A (both situated in hippocampus) brought on by PTSD cum anxiety treatment. Pertinently, in mice treated with LPS, minimizing the astroglial Kir4.1 expression (hippocampal) improved depressive-like behaviours and promoted fear decimation. TNF-alpha was also injected intra-cerebroventricularly, which impaired relevant fear amelioration and increased Kir4.1 expression. The combined results of the study exhibit fascinating safeguarding effects of Rg1 countering the PTSD-like behaviors in rodent, probably through advancing synaptic proteins and lowering TNF-α and Kir4.1 in the hippocampus (Zhang, Z. et al., 2021).

3.2. Hepatic diseases

Rg1 decreases blood levels of aspartate transaminase (AST), alanine transaminase (ALT) and alkaline phosphatase (ALP) whilst, improves

the magnitude of hepatic fibrosis indicators in addition to the the proportion of hydroxyproline (liver) in rats with thioacetamide-induced liver fibrosis (ALP). Rg1 definitely prevents platelet-derived growth factor-BB-stimulated hepatic stellate cells from proliferating, activating, and producing ROS (Geng et al., 2010). Through the NF-B signalling system, pretreatment of Rg1 lowers apoptosis of hepatocellular origin and prevents an inflammatory counter-reaction in ischemia reperfusion injury (Tao et al., 2014). Rg1 encourages GR, which mediates the regulation of NF-B, and suppresses inflammatory compensatory resposes in the mouse model of alcohol orchastrated hepatitis (Gao et al., 2015). Rg1 reduces the increase of plasma aminotransferases and ameliorates liver histological abnormalities in carbon tetrachloride (CCl4)-induced Hepatic impairment in mice (Xin et al., 2016). Actually, in human hepatoma cells, Rg1 also inhibits the LKB1/AMPK/FoxO1 pathway's capability to generate liver glucose (Kim et al., 2010). In addition, Rg1 has pharmacological protective effects in rats against pulmonary fibrosis brought on by bleomycin, which may be connected to the the up-regulation of Cav-1 whilst the TGF-1 down-regulates (Zhan et al., 2016). Finally, Rg1 significantly reduces the hepatic damage brought on by LPS/GalN (Komatsu et al., 2012). Rg1 modifies the regulation of HDL triglycerides and LDL cholesterol in an NAFLD (no alcoholic fatty liver disease) cell model, which drastically lowers the contents of HMG-CoA reductase and SREBP-2 whilst increasing the contents of CYP7-alpha (Jiang et al., 2015).

A widely used antipyretic and painkiller, acetaminophen (APAP) is also a prototype hepatotoxicant. APAP is renounced for instigating drug-induced liver damage (DILI). In the US and Europe, DILI is the formost reason for liver failure, and the majority of cases of DILI are brought on by temporary or recurring APAP abuse. The distinctive centrilobular hepatic necrosis that APAP causes is a result of CYP2E1 being overexpressed. In actuality, APAP is sulfated and glucuronidated, although a minor amount is activated metabolically by CYP2E1 to become N-acetyl-p-benzoquinone imine (NAPQI). Despite the fact that APAP is a prescription medication, hepatotoxicity at large doses needs to be avoided with considerably greater care. It's interesting to note that Rg3 prevents the production of hazardous intermediate by reducing the expression of CYP2E1 in APAP-induced liver damage (Gum and Cho, 2013). Instead of harming liver function, these ginsenosides help mitigate APAP-induced liver damage.

Alcoholic cirrhosis, alcoholic hepatitis, alcoholic fatty liver, and even hepatic neoplasia are all examples of ethanol-induced hepatic damage. While Rg1 therapy generates protective benefits against the negative effects of ethanol consumption by lowering the generation of Malondialdehyde (MDA) and oxidative stress, chronic ethanol-induced liver damage results in a rise of serum AST, ALT, ALP, and LDH (Korivi et al., 2012). Additionally, TGF-1 and collagen fiber deposition, which are often seen to increase in rat models, are reduced by Rg1 (Xie et al., 2010). Particularly, Rg1 greatly enhances liver function in a variety of ways while also reducing pathological damage. Rg1 effectively suppresses collagen deposition and ROS generation in the liver and blood. A liver toxin called CCl4 is triggered by CYPs (Cytochrome-P) to produce the trichloromethyl radical (Huu Tung et al., 2012). In reality, the CCl4-induced liver tempering model has been widely employed across the world to evaluate the therapeutic impact of putative hepatoprotective drugs. In mice treated with CCl4, ginseng reduces the turnover of inflammatory CKs including IFN-γ, IL-1, and chemokines like MIP-2, MCP-1 and KC (Shim et al., 2010). Additionally, ginsengs restore the activities of the enzymes viz, Catalase and superoxide dismutase (SOD) in the hepatocytes, mediate Histological integrity, biochemical and physiological parameters in rodents treated with a toxin, and shield rats from an increase in ALP, LDH, AST, ALT and liver peroxide levels (Li, J.-p. et al., 2014). The P450-associated monooxygenase activities are specifically inhibited by ginseng saponins in a dose-dependent manner (Olsen et al., 2015). Additionally, the lipid peroxidation mediated by CCl4 in mouse hepatic microsomes is significantly influenced by saponin's inhibitory actions on P450 enzymes (Xin et al., 2016). These successfully raise the content of IL-10 while decreasing the abnormal alterations of NFκB, IL-6, IL-1, and TNF-α (Zou et al., 2013). Further, Rg1 promotes Nrf2 activation and increases the expression of, in Rodent CCL-4 in incurred liver fibrosis, antioxidant enzymes thereby acting as a pharmacological protective factor. Due to its extensive usage in worldwide sectors including pigments, electronic components, fertilizers and electric batteries, Cd as in manifestation of

CdCl2, is widely distributed in the environment. The adverse effects of CdCl2 exposure include severe organ malfunction (Park et al., 2013). When not digested, heavy metals like cadmium accumulate in human tissues and become poisonous. Ginsenosides, on the other hand, enhance CdCl2-suppresses body weight growth and reverses the liver's decreased glutathione (GSH) content following CdCl2.

Raise in the serum ALP and GSH level, lowered the elevated LPO (lipid peroxide) ALT and ASTmlevels caused by cadmium (CdCl2), and provide treatment (Huu Tung et al., 2012). In a similar study, the reversal of histopathological abnormalities and inhibition of pro-apoptotic (Bad) protein in hepatocellular milieu, showed red ginseng's hepatoprotective capabilities. A small amount of anti-oxidative and anti-apoptotic substances are involved (Park et al., 2013). Inhibition of activation of the NLRP3 inflammasome and the ER stress counter-response and may be advantageous for the management, even treatment of NAFLD. The production of IL-18 and IL-1, NLRP3 inflammasome activity, and the NAFLD model all rise in one HFD. Additionally, Rg1 blocks the reactions, indicating that one possible way it can lessen inflammation is by blocking the inflammasome (Xu et al., 2018).

3.3. Pancreatic diseases

In Asia, ginseng has been employed as an anti-diabetic plant for thousands of years and has potent active components. Since growing data indicates that ginseng saponins enhance IR (insulin resistance) via reducing intracellular TC (Triglycerides) buildup, ginseng root is well recognized for accelerating anti-diabetic action (Zhai et al., 2018). Existing research indicates that the main mode of -cell death in DM is apoptosis. Rg1 inhibits the production of the Fas gene in stimuli-induced apoptotic cells because the Fas signal pathway and mitochondrial stress are mostly associated to the anti-DM activity (Chen et al., 2012). Rg1 dramatically reduces pancreatic wet weight and visceral index as well as fasting blood glucose in a rat model of pancreas injury brought on by D-galactose. Further, Rg1 therapy dramatically increases SOD and total antioxidant capacity activity while considerably decreasing the integral optical density of advanced glycation end products in pancreatic tissue and MDA concentration. In the triglyceride accumulation scenario, Rg1 increases the expression of IRS-2 to boost the activation of the insulin/IGF-1 pathway, which in turn boosts glucose-stimulated insulin secretion and cell survival in the Min6 cell line (Park et al., 2008).

3.4. Diabetes mellitus

One kind of metabolic disorder called DM is characterized by dyslipidemia, hyperinsulinemia, and hyperglycemia that is mostly brought on by IR. Additionally, DM is a major contributor to current neurological illnesses. The problem of IR, which is defined by a compromised insulin signalling system, presents itself in the management of DM. Numerous indicators point to the presence of subclinical chronic inflammation in T2DM patients (Zhai et al., 2018). It is important to highlight that Rg1 has a cascade protective effect by promoting the Akt/Nrf2/HO-1 cascade, lowering ROS homeostatic perturbation, preventing NLRP3 inflammasome wakeup, and minimising the incidence of inflammatory process. Insulin stimulates adipocytes' absorption of glucose in adipose tissue via the IRS-1/PI3K/Akt mechanization (Chen, W. et al., 2016). However, Rb1 inhibits the release of ER stress and the consequent TXNIP/NLRP3 relevant inflammasome, which lessens insulin resistance (IR) by promoting the insulin-PI3K signalling mechanism (Gao et al., 2020).

3.5 Anti-inflammatory activity

Both the adaptive and innate immune responses involve inflammation, a common reaction to infection. The primary characteristics of inflammation include Hyperthermia, irritation, pain, erythema, inflammation, and functio lessia (Yang et al., 2015). Ginseng may have some Antinflammatory effect, according to a variety of in-vivo, in vitro and even clinical trials (Choi et al., 2018; Kim et al., 2017; Kim et al., 2018; Lee, J.H. et al., 2018; Lee, M.J. et al., 2018). Ginsenosides Rp1 and Re have the capability to inhibit the NF-κB signalling cascade, according to research by Kim DH et al. (Kim, D.-H., 2018). In a different investigation, Yu et colleagues found that ginsenoside Rc can prevent macrophage-derived cytokines from being expressed (Yu, T. et al., 2017). Additionally, in activated RAW264.7 macrophages, HEK293 cells, human synovial cells it can restrict the stimulation of p38/ATF-2 signaling, , IB kinase /interferon regulatory factor-3 in addition to TNF receptor-linked factor family member-associated NF-kappa-B activator (TANK)-binding kinase-1 (Han et al., 2018; Yu, T.

et al., 2017). IL-6 and TNF-α production influenced by lipopolysaccharide (LPS) was suppressed by a P. notoginseng extract in a concentration-dependent pattern, according to research done in 2006 by Rhule et al on cultured RAW264.7 macrophages (Rhule et al., 2006). It's interesting to note that a clinical investigation found that individuals who were administered ginseng following ameliorative surgery had an approximately 35% greater likelihood of being disease-free for a period of 5 years and a enjoyed circa 38% higher survival rate than those who didn't go through the regimen(Ahn et al., 2006).

A clinical experiment involving 18 male college students was conducted to determine if KRG (Korean Ginseng) consumption may affect exercise-induced muscle degradation and inflammation incurring events (uphill treadmill running). After exercise or throughout the recovery period, the plasma concentrations of IL-6, glucose, insulin, and creatine kinase were lower in the participants who received Panax ginseng extract. These findings imply that KRG supplementation may prevent muscle damage and inflammatory reactions brought on by exercise, therefore enhancing insulin sensitivity (Jung et al., 2011). To examine the impact, a randomised double-blind placebo-controlled crossover trial, of Rg1 on IL-10 and TNF-α gene expression with in the human skeletal muscles post exercise exertion and its impact in relation to the ergogenic responses. The results showed that Rg1 have the tendency to repress exercise mediated increment of thio-barbituric acid (TBA) reactive substance and overturn the elevation of TNF-α as well as the decline of IL-10 mRNA within the quadriceps muscles vis-a-vis exercise contest. (Hou et al., 2015). Moreover, In a clinical trial with 96 NSCLC- neoplasia incidents, researchers determined that ginseng constituents can trigger the release of INF-γ and IL-2 (Th1 CKs), in addition to the ratio of IL-2/IL-5 and INF-γ/IL-4 (Th1/Th2) of CKs, while decreasing Th2 cytokines (IL-4 and 5), and functional analyses of cancer therapy-lung scores. This suggests that ginseng polysaccharides can favorably impact immune function pertaining to NSCLC patients (Ma et al., 2014).

3.6. Antimicrobial activity

Development of new types of antimicrobial drugs is urgently needed since antibiotic resistance is on the upsurge (Roca et al., 2015; Yoo et al., 2012). In this situation, new antibacterial drugs would be welcomed, especially those derived from herbal sources. According to several investigations, ginseng extract or its individual components or their combination have antimicrobial and/or antiviral capabilities. Korean Red Ginseng (KRG) extract reduced lung illness in mice by decreasing inflammatory cytokines brought on by respiratory syncytial virus (RSV) and by raising levels of CD8+ T cells, IFN-γ and even CD11c + dendritic cells [49,50]. In a different investigation, the antiviral cytokines IFN- and IFN- were induced by the ginsenosides Re, Rh1, Rg2, Rb1, Rb2, Rc, Rd, Rg3(s), Rg1, Rf, Rg2(s), Rg2(r), and Rg3 in a counteraction to H5N1 influenza virus infection [51]. Additionally, H3N2, H1N1, and H9N2 influenza viruses are all susceptible to this herb's effects (Yoo et al., 2012). In patients diagnosed with HIV type-1 infection, a clinical investigation found that KRG reduced the antigen level of blood circulating CD8 and delayed the loss of CD4 T cells (Cho and Kim, 2017) (Ratan et al., 2021)

3.6. Anti-obesity

An inconsistency among energy input and output leads to overwhelming quantity of energy being stored in adipose tissue in form of triglycerides, which constitutes a major health hazard (Jung and Choi, 2014). Past few decades have observed, a significant elevation in the incidence of obesity and its metabolic side effects worldwide. Of approximately 2 Bn overweight populatin globally, 1 in every 3 is obese as per the World Health Organization report (Seidell and Halberstadt, 2015). The utilization of natural remedies in the management of obesity has garnered immense of attention lately and is regarded as a powerful strategy for controlling fat. The primary active ingredients of ginseng, ginsenosides, have inherent in and have demonstrated the most anti-obesity benefits in prior research. According to research, ginsenoside Rb2 can successfully lower body mass in diet-induced obese (DIO) mice thereby enhancing the insulin sensitivity, and increasing the energy dissipation efficiency (Hong et al., 2019). Additionally, it was found that ginsenoside Rh1 reduced plasma triglyceride levels and decreased body and epididymal fat density surge in DIO mice (Gu et al., 2013). Additionally, some studies examine how ginsenosides affect food intake and, interestingly, discover that their appetite-suppressing benefits are really caused by an increase in central leptin susceptibility (Wu et al.,

2014). To maintain energy balance, the hormone leptin packaged and released by adipocytes, impart impact on sites in the arcuate nucleus (hypothalamus) to regulate appetite (Li and Ji, 2018). When obesity is generated by a high-fat diet (HFD), a different analysis revealed that the ginsenoside specifically Rb1 can reduce the urge for nourishment via the modulation towards Neuropeptide Y and serum peptide YY (Lin et al., 2014).

In terms of lipid homeostasis and energy balance, adipocytes are crucial to the development of obesity. Pre-adipocytes differentiate into adipocytes through a complex process known as adipogenesis (Mota de Sá et al., 2017). In mammalian cells, fatty acid synthase (FAS), fatty acid binding protein 4 (FABP4) and adiponectin are thought to be the key perpetrators of adipogenesis relevant to fully matured fat cells, whilst peroxisome CCAAT/enhancer binding proteins (C/EBPs) viz. C/EBP α, β and δ and proliferator-activated receptor γ (PPAR γ) are expected to be the essential regulators pertaining to initial phases (Moseti et al., 2016). Ginsenosides like Rc, F2, Rg1, Rg2, Rb1, Rh1 and Rg3 have been shown in multifarious appraisals to be effective in suppressing fat cell production or adipogenesis in 3T3-L1 pre-adipocytes. Additionally, they can stop the deposition of triglycerides and reduce lipid synthesis, adipocyte size, and adipose weight. The desensitization of the protein expression of adipogenesis contributing transcription factors as well the primary lipogenic enzymes, in the 3T3-L1 cells might as well be connected to the molecular management of ginsenosides on adipogenesis. As per data analysis, ginsenosides mostly inhibit PPAR-related circuits whilst upregulating AMPK, the adenosine monophosphate-activated protein kinase. mechanism route (Lee, K. et al., 2019). Likewise, in vitro research revealed that ginsenoside F1 significantly antagonized the output of reactive oxygen species (ROS) as well as triglyceride content during adipocyte development (Simu et al., 2017). White adipocyte tissue (WAT) browning has recently drawn a lot of attention because of its possible relevance in the fight against obesity. A putative Lipolytic and thermogenic medicinal drug, Rb1 has been shown to enhance browning by the way of modulation of PPAR γ (Lim et al., 2019).

Through activating the AMPK cascade, ginsenosides can also reduce fat biosynthesis and increase energy utilization by the liver. In obesity begot diabetic db/db mice, ginsenoside Rb1 can improve sensitivity to insulin and plummet the hepatic fat accumulation. These benefits were complemented by decreased Hepatic triglycerides levels and liver mass. Moreover, it decreased the amount of unbound fatty acids found in obese mice, which probably have decreased hepatic lipid buildup (Yu et al., 2015). Another study found that Rb1 could decrease fatty liver in obese rats by triggering AMPK (Shen et al., 2013). Ginsenosides Rg3 and Rg1 have been shown in in vitro tests to instigate the AMPK pathway, elevate the levels of phospho-acetyl-CoA carboxylase and p-AMPK, and block the production of cholesterol and gluconeogenesis (Chang et al., 2013).

According to several findings, inflammation is the most important factor in the numerous problems related to obesity due to the unexpected overlap between metabolic inadditon to inflammatory sensors and their corresponding downstream tissue responses (Lumeng and Saltiel, 2011). TNF- α, IL-1β, and IL-6 expression, together with macrophage antigen, F4/80 and CD68, were all reported to be inhibited by ginsenoside Rh1 (Gu et al., 2013). Another study found that ginsenoside Rb1 can reduce the levels linked to NF-κB cascade molecules and IL-6, TNF-α, and/or IL-1β (Wu et al., 2014). In an in vitro investigation, ginsenoside Rb1 significantly reduced inflammation and oxidative stress brought on by free fatty acids in 3T3-L1 cells (Wang et al., 2017). Intriguingly, adipose succinate proximate NLRP3 inflammasome actuation may be the therapeutic motif for reducing lipolysis and IR. Ginsenoside Rb2, Rg5 and Rg1 can also prevent IR and increase serum glucose metabolism to play a role in anti-obesity. Furthermore, ginsenosides Rd, Rg1 Ro, Rb1, Rg3, in confluence to compound K were substantiated to drastically deescalate pancreatic lipase activity. However, the pancreatic lipase antagonists can control the obesity by increasing fat elimination into faeces (Fan et al., 2020; Yu, H. et al., 2017).

3.8 COVID – 19

Despite these fruitful investigations, there hasn't yet been any concrete proof that ginseng can prevent SARS-CoV-2 and lessen COVID-19 symptoms. Additionally, there is a great need for ginsenosides and saponins that can reduce COVID-19 symptoms by preventing

inflammasome start. Following the discovery of SARS-CoV-2 as the dreadful virus driving the continuing worldwide COVID-19 pandemic, much effort has been put to comprehend the pathogenesis of COVID-19 infection by SARS-CoV-2 and the underlying processes in COVID-19 patients. This initiative has effectively shown that, despite instances of moderate asymptomatic COVID-19 brought on by SARS-CoV-2, SARS-CoV-2 also powerfully engages the immune response of the host, causing hyper-inflammation and a cytokine storm that eventuates in severe COVID-19, organ damage, and even fatality (Merad and Martin, 2020). Inflammasome activation, which triggers pyroptosis via the GSDMD pores and the dissemination of the CKs, through the GSDMD pores, is one of the most significant markers of inflammatory counter-response as well as disease pathogenesis (Xue et al., 2019; Zheng et al., 2020). Numerous inflammasomes are activated by SARS-CoV-2, which causes severe COVID-19 in many patients coupled with irreversible multiple organ damage as a result of pyroptotic cell death and cytokine storms brought on by the large release of pro-inflammatory CKs. Contrary to these discoveries, multiple investigations have demonstrated the inhibitory effect of SARS-CoV-2 in Inflammasome activation to evade host antiviral defense. Restricting Inflammasome activation as well as improving host immunity in relation to COVID-19 patients can give clinical efficacy.

Numerous inflammatory illnesses have been shown to be improved by ginseng and its primary physiological and pharmacological ingredients, ginsenosides and saponins, which have been effectively proven as nutraceuticals by attenuating the priming stage of inflammatory surge (Lee et al., 2021). It's interesting to note that saponins and ginsenosides both reduce inflammasome activation to limit the triggering phase (Yi, 2021). This offers compelling evidence that regular ginseng supplementation may lower predisposition to COVID-19 evolution, and that ginseng and its chemical components, ginsenosides and saponins, may be useful as herbal remedies to treat COVID-19 by preventing inflammasome arousal. Prominently, ginseng can reduce COVID-19 by a unique method that involves blocking inflammasome activation and boosting the host's antiviral defenses (Hyun et al., 2021). In **Fig. 4**, ginseng's ability to treat and prevent COVID-19 through regulating inflammasome activation is depicted.

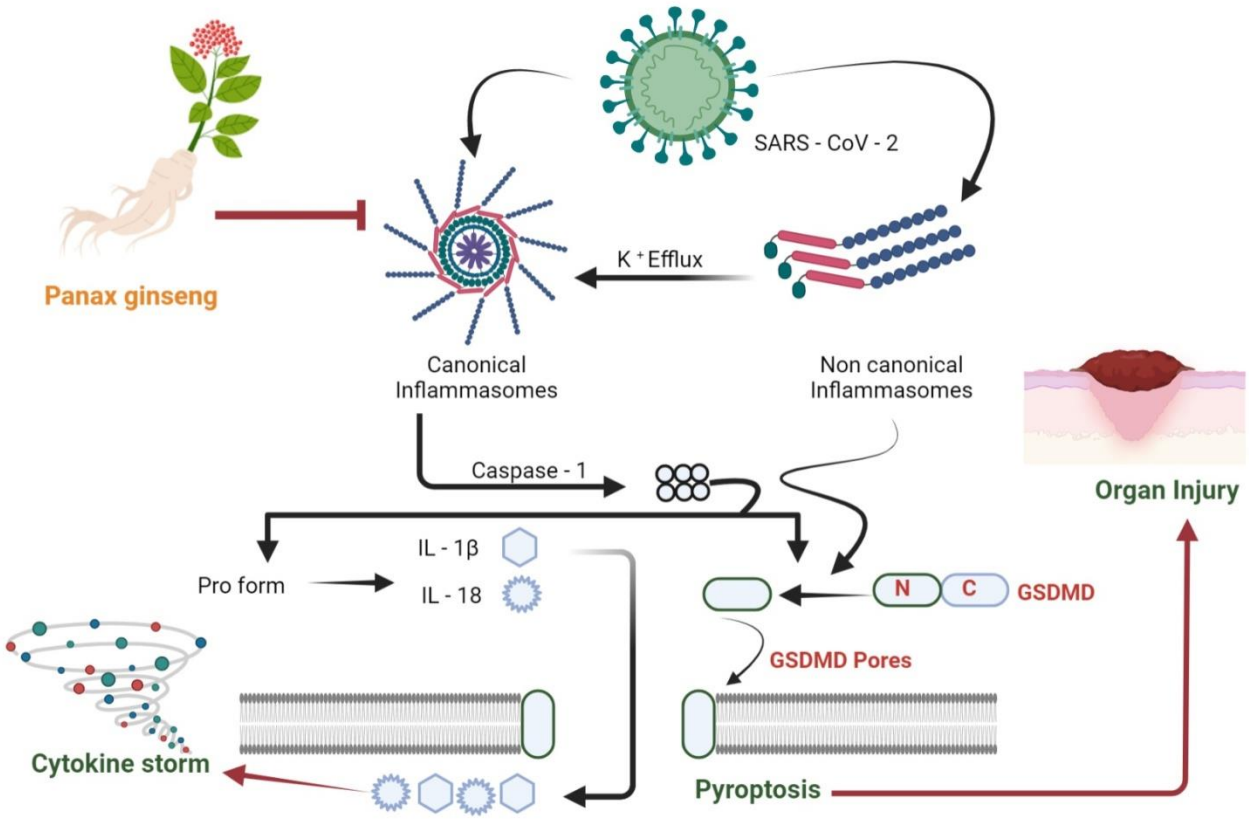


Figure 4: Shows a graphic description of the possible functions of ginseng in COVID-19 afflicted with SARS-CoV-2. Via activating both canonical and non-canonical inflammasomes, SARS-CoV-2 infection causes organ damage by pyroptosis in amalgamation to initiating a cytokine storm by enormous levels of cytokine production. Ginseng controls inflammasome activity, which may be advantageous in tackling against SARS-COV-2 (COVID-19) (Yi, 2022).

Numerous analyses have shown that ginseng, a typical herbal remedy, its constituents, and medications constituting ginseng can effectively inhibit pro-inflammatory CKs (like TNF-alpha, IL-1 and IL-6), as well as anti-inflammatory CKs (like IL-10 and TGF-), by positively modulating signalling cascades like JAK/STAT, NF-kB, MAPKs. Choi JH (2022), discussed the mechanisms underlying the COVID 19 progression and basing that as an edifice that postulated the COVID 19 potential of the KRG (Korean ginseng), thereby advocating for the potential of the said plant in managing the enigma that is COVID-19 (Choi et al., 2022).

Investigators introduced drug encased albumin NPd as a treatment modality to treat the severe SARS-CoV-2 patients' dreaded prognosis. The steroidal ginsenoside-saponins PNAB-Rg6 and PNAB-Rgx365 were employed to increase sustained bioactivity using PEGylated nanoparticle albumin-bound (PNAB). Our findings show that administration of PNAB-steroidal ginsenoside to SARS-CoV-2 patients admitted in the ICU. The foregoing ginsenosidal formulation, with in the PBMCs (Peripheral blood mononuclear cells) of critical patients, efficiently reduces histone H4 and NETosis (Neutrophil extracellular trap formation) related variables in the plasma and reduces SREBP2 influence systemic inflammation. The modified blood vessel model verified that these medications are successful in reducing vascular inflammation and blood clot formation. Additionally, in vivo experiment demonstrated that these medications work to increase survival rates by reducing tissue detriment and cytokine storm. Overall, their research pointed to the possibility of using these PNAB-steroidal ginsenoside medications to treat severe SARS-CoV-2 manifestations the likes of coagulation and cytokine storm (Park et al., 2021).

According to REF, the mechanism of the ginseng plant indicates that the primary active components of Panax ginseng, 20(R)-ginsenoside Rg3 and 20(S)-ginsenoside Rg3, effectively block the RBD (Receptor binding domain) of SARS-CoV-2 spike glycoproteins, hence deterring a viral infection. In other words, treatment with aforementioned two ginsenosides suggests that it may be possible to lower the risk of viral infection by preventing the interaction between ACE2 produced in cardiomyocytes and the RBD of SARS-CoV-2 spike glycoproteins. By targeting areas of receptors per SARS-CoV-2 spike that are inaccessible to inherent macromolecules, the 20(S)-ginsenoside Rg3 along with 20(R)-ginsenoside Rg3 efficiently prevent binding with ACE2, the likes of which are elusive to immunological antibodies. According to these findings, the foregoing Rg3 ginsenosides can prevent SARSCoV-2's intracellular invasion and preserve the myocardium following the SARS-CoV-2 infection. This goes to show that the SARS-CoV-2 outbreaks that are now endangering human health around the globe can be efficiently warded off by the ginsenosides in concern. Additionally, SARS-COV-2 always causes systemic inflammation. It is well known that ginsenoside, an active component of ginseng, has anti-inflammatory properties. This further augmented that ginsenoside has counter-inflammatory effect in macrophages that are otherwise the immune cells in the body. Ginsenoside suppressed cytokine expression (TNF-, IL-1, IL-6) (Kim et al., 2017). The researcher attributes this effect to ameliorating the COVID 19 pertained systemic inflammation. Similarly, Hossain MA (2022) pleads the case in favour of COVID 19 manifested Coronary artery dysfunction and arrhythmias (Hossain and Kim, 2022). Notwithstanding the foregoing theoretical evidence, nothing accounts for the fact that there hasn't been a clinical study to substantiate the claim.

3.9. Sepsis

Rb1 is the main ginsenoside present in P. ginseng, which is commonly utilized as a conventional medicine in Asia. Rb1 has been discovered to defend against sepsis-induced liver and lung damage, including pneumonia. Its effects on inflammation purport to be primarily mediated through NF-κB activity modulation. TLR4 and inflammatory markers, particularly NF-κB p65, were both dramatically inhibited by Rb1 in the lung, which resulted in lower levels of

IL-1β, TNF-α and IL-6. Both Rb1 and 2, dramatically lowered IL-6 and TNF-α levels dose-dependently (Yu, S. et al., 2017). In addition, Rb1 was ascertained to limit TLR2 function, decrease p65, ERK, and JNK phosphorylation (Joh et al., 2011). These results imply that Rb1 may function via lowering NF-B activity. Rb1 was found to block the production of TNF-α and NF-κB in a rat model of septic shock, protect the lung and liver, regulate BP (Blood pressure), and improve survival (Shaukat et al., 2019).

Ginseng protopanaxatriol Re is frequently employed as a counter-inflammatory. Re ginsenoside, owing to retrospective analyses have a potential to curb inflammatory responses in revulsive hepatocytes and may instantiate blockade of IKK-β (Hua et al., 2020; Shaukat et al., 2019). Re has been proven to constrain excitation by the way of restricting the phosphorylation, decrease the levels of pro-inflammatory proteins such iNOS, TNF-α, COX-2, IL-1, and IL-6, in addition to lowering the NO generation. Re has also been shown to diminish inflammation in RAW264.7 cells. Re also blocked the phosphorylation of many MAPK translated proteins, including c-JNK, ERK1/2, and p38, as well as the NF-κB associated proteins p65 and IB (Quan et al., 2019). In addition, Re stopped the phosphorylation of IRAK-1 and the degradation of IRAK-4, as well as the TLR-LPS interaction. Myocardial contractility is often decreased in sepsis and septic shock, which negatively impacts heart normalcy. By selectively modulating NF-κB activation as well as MAPK signaling, Re was shown to prevent these effects , and comparable results were observed in lung tissue (Chen, R.-C. et al., 2016). These findings show that Re has a beneficial effect on both lung and heart health.

Following consumption of P. ginseng, bacteria in the microbiome create the Rb1 metabolite compound K (CK). In LPS-induced inflammation, CK inhibits competitively the NF-κB nuclear translocation, GC-GR (Glucocorticoid and its receptor) connection, MAPK phosphorylation and IκB-α phosphorylation in addition to other inflammatory processes. Additionally, it has been demonstrated that CK suppresses iNOS, decreases COX-2 transcriptional and translational expression, and inhibits the generation of NO, IL-1β and finally the IL-6 (Lee, J.H. et al., 2018). The drug was also utilized to target LPS-activated RAW264.7 cells using a composite of CopA3 co- gold nanoparticles (GNP-CK-CopA3), which attenuated both NF-B and MAPK activation (Liu et al., 2020). Additionally, it has been noted that CK can reduce sepsis symptoms by controlling the TLR4 signaling that GR induces. This includes blocking of NF-B and MAPK signaling, as well as the fabrication of pro-inflammatory cytokines, and competitively inhibiting GR's ability to bind to the artificial GC dexamethasone, thereby exciting GRE. The disruption of p65/interferon regulatory factor interaction was shown to be the mechanism behind this inhibition of inflammation-related gene expression. Notably, CK inhibited the production of pro-inflammatory cytokines in LPS-treated mouse models of septic shock (Liu et al., 2008).

Particularly in Korean Red ginseng, the protopanaxatriol-type ginsenoside Rh1 is present. Owing to the regulation of NF-κB signal transduction, KRG has been seen to regulate immunological activity, inflammation, and stress (Nguyen et al., 2021). Cascade Rh1 has been discovered to affect the levels of iNOS and COX-2 protein as well as suppress IFN-γ and NF-κB mediated JAK/STAT and ERK activation (Jung et al., 2010). Rh1 also prevented pyroptosis in confluence to IL-1β production and stopped the effectuation of the AIM2 and NLRP3 inflammasomes during macrophage mediated inflammation (Kim et al., 2014; Li, J. et al., 2014). Dexamethasone's anti-inflammatory properties were similarly enhanced by Rh1 without causing hyperglycemia as an adverse impact. Remarkably, the amalgamation of Rh1 and dexamethasone dramatically decreased the levels of IL-17, IL-6 and TNF-α, with comparable effects found for IL-17 and IL-6, even post long-term dexamethasone usage (Lee, W. et al., 2019; Li, J. et al., 2014). Additionally, it has been proposed that Rh1 may target HMGB1, a sepsis arbitrator, thereby subduing sepsis. Rh1 decreased plasma levels of IL-6, TNF-α and IL-6 whilst also incurring the ERK ½ and NF-κB and activation by HMGB1, as well as minimizing HMGB1 exudation after Cecal ligation and puncture in vivo, thereby reducing sepsis and tissue damage (Lee, W. et al., 2019).

The anti-inflammatory and anti-allergic properties of ginsenoside Rh2 are notable. Rh2 has been observed to have counter-inflammatory implications in animal models of acute lung injury, protecting from damage brought on by LPS. The substance reduced the levels of COX-2, iNOS, Pro-inflammation NO, p38, TNF-α, and IL-1β , whist also inhibiting the phosphorylation of IB-, ERK, and JNK, whereas increasing the

production of counter-inflammatory CKs (IL-4, 6, and 10) and ameliorating the histological tempering (Baatar et al., 2018; Hsieh et al., 2018). The immensely soluble sulfated renditons of Rh2-B1 and Rh2-B2, which in turn considerably restricts the release of TNF-α, IL-6, NO and IL-1β as well as contrastingly limiting MAPK and NF-κB signaling, were used to increase these anti-inflammatory effects. This suggests that sulfated ginsenosides may have the ability to treat sepsis (Fu et al., 2013).

Ginsenoside Rg1 has been successfully utilized to treat immune-related diseases and inflammation (Zou et al., 2013). Rg1 is well recognized for defending against cardiac problems and pulmonary damage brought on by sepsis. The substance greatly increases the synthesis of the counter-inflammatory CK IL-10 while dramatically decreasing the release of CKs including TNF-α, IL-6, IL-1β, and iNOS (Ning et al., 2018). Rg1 was found to improve lung damage and increase lifespan in animal models by decreasing pro-inflammatory cytokine release (Wang et al., 2019). In LPS-treated animals, Rg1 also improved cardiac performance and decreased apoptosis and inflammation, while down-regulating concentrations of pro-inflammatory CKs including but not limited to TLR4, NF-κB, and NLRP3 (Luo et al., 2020). Similar to the effects of dexamethasone, P-65 DNA adsorption and the nuclear translocation of NF-κB was decreased, along with ERk, JNK, MAPK and p38 phosphorylation. Additionally capable of binding GR, Rg1 can increase the Inflammation rectification by the GCs (Song et al., 2013). The drug also has fewer adverse effects and doesn't cause immune-related weight loss, hyperglycemia, or osteoporosis (Du et al., 2011). It has also been suggested to prevent inflammasome triggering, which would prevent pyroptosis as well as elevated IL-1β levels (Kim et al., 2014). The TLR4-NF-κBB-NLRP3 cascade inhibition may have been could safely be attributed to these consequences.

Black ginseng has several key components, one of which is ginsenoside Rg5. NF-κBIt has also been discovered to reduce levels of the pro-inflammatory CKs IL-1β and TNF-α, as well as the inflammation relevant proteins and enzymes including the COX-2 and iNOS, and to prevent NF-κB actuation when analyzed in a model likened to LPS-treated alveolar macrophages. Additionally, the substance was shown to lessen IRAK-1 and IKK-β phosphorylation while also reducing IRAK-1 and IRAK-4 disintegration following LPS treatment. The synthesis of HMGB1, in addition to its influence on the WBCs (leukocytes), tissue tempering, and survival in mice, were decreased via the activation of NF-κB and ERK 1/2 albeit reducing the of TNF-α and IL-6 levels (Kim et al., 2019; Kim et al., 2012). Additionally, both p65 nuclear translocation and NF-κB phosphorylation were curtailed (Kim et al., 2012).

Red ginseng contains the tetracyclic triterpenoid known as Rg3. Rg3 inhibits inflammation via activating NLRP3 and the MAPK and AMPK pathways. Rg3 reduces the concentrations of IL-6, TNF-a and IL-1β together with NO and ROS (Shin et al., 2013). The decrease of NLRP3's S-nitrosylation by NO inhibits the NLRP3 inflammasome (Yoon et al., 2015). Rg3 can also inhibit the release of IL-1β and the triggering of caspase-1 (Xin et al., 2019), while encouraging macrophage mediated phagocytosis of bacteria wherein it activated the ERK1/2 and p38/MAPK cascades. By lowering ROS concentration in body and increasing the translation of transcription factors that promote the expression of genes involved in mitochondrial genesis and restoration, sepsis frequently results in mitochondrial damage, which Rg3 can alleviate (Lee et al., 2013). Additionally, Rg3 prevents sepsis-induced cellular and organ pathology by controlling autophagy via switching on the AMPK signaling and can reduce mitochondrial damage (Xing et al., 2017). These results demonstrate that Rg3 safeguards against lung damage by lowering pro-inflammatory factor levels and increasing anti-inflammatory factor levels (Yang et al., 2018).

There is a curious relationship between Sepsis and COVID-19. The preponderance of ICU fatalities from Coronavirus Disease 2019 (COVID-19) are believed to be connected to sepsis (Beltrán-García et al., 2020). Sepsis usually develops as a result of COVID-19. It is important to note that ginsenosides may have therapeutic benefits for COVID-19. Natural substances, such as 20(R)-ginsenoside Rg3, have been said to be able to block the entrance of viruses like SARS-CoV-2 (Zhang, D. et al., 2021). Patients with COVID-19 frequently experience cytokine storms (Mehta et al., 2020), and their peripheral blood mononuclear cells (PBMCs) have comparable high cytokine levels. It was discovered that using PNAB-Rg6, a PEGylated Nanoparticle Albumin-Bound (PNAB)-steroidal Ginsenoside, dramatically decreased the CK levels and

decreased PBMC related turnover of pro-inflammatory CKs. Moreover, the PNAB-Rg6 was discovered by PCR analysis to decrease the mRNA levels of inflammation pertaining genes, the likes of NRLP3 (Park et al., 2021; Xiao et al., 2019). NF-κB nuclear translocation is reported to be blocked by ginsenosides (Xiao et al., 2019). MAPK/NF-κB signalling regulates IL-6 synthesis, and overly high IL-6 is closely linked to COVID-19 mortality (Zhou, P. et al., 2020). When up-regulated the IL-6 amplifier, may encourage a CK storm, is a significant cause of inflammation. This raises the prospect that inhibiting the IL-6 amplifier's activity might stop the cytokine storms that are present in severe COVID-19 (Hirano and Murakami, 2020). Additionally, it appears that ACE2 interactions with viruses activate the inflammasome, which might increase inflammation by triggering inflammatory cascades (Divani et al., 2020). High quantities of ginsenosides can suppress the SARS-COV-2 to ACE-II (Angiotensin II) interaction, which lowers the generation of IFN-I. This shows ginsenosides may be used in COVID-19 treatment. Additionally, ginsenosides have a limited ability to prevent inflammasome activation. A common cascade including the cytoplasmic phosphorylation of I-κB, its subsequent ubiquitination and degradation, and the release as well as nuclear entry of NF-κB can be formed by these diverse signals. Ginsenosides work by stopping the breakdown of IκB, which keeps NF-κB in the cytoplasmic milieu where it cannot activate the transcription of pro-inflammatory proteins (Yu et al., 2022).

4. Mechanisms of Ginsenosides an anti platelet agent

Ginsenosides are the principal pharmacologically active parts of ginseng and have been proven to offer a wide range of preventive and treatment benefits for CVD management. The majority of the assessed ginsenosides, which number over 40, are Ro, Rp 1-4, Rc, Rb1-2, Rf, Rd, Re, Rg1-3 and Rh1-2. Based on their molecular orientations, these ginsenosides are classified as PPD, PPT, and Oleanane kinds (Kim, J.-H., 2018).

4.1. Ginsenoside, G-Rg1-2

Rg1 and Rg2 have been shown to have mild antiplatelet effects against ADP at 20 μM, collagen at 10 mg/mL, arachidonic acid (AA) at 100 μM, platelet-activating factor (PAF) at 2 ng/mL in addition to activating rabbit and human platelets in a prior investigation. These effects were measured by the suppression of ATP dissemination. Additionally, Rg2 lowered Ca2+ traversion (Kim, J.-H., 2018). Following that, the Rg1 at a dose of 4 mg/mL was tested for its anti-thrombotic impacts on mammalian thrombocytes versus collagen at 1 and 2 μg/mL, U46619 at 0.3 and 0.6 μM, ADP at 10 and 20 μM and eventually thrombin at 0.05 and 0.1 U/mL. Zhou et al (Zhou et al., 2014), discovered that Rg1 significantly inhibited platelet agglutination at both the levels of agonist concentrations, albeit the suppression was more pronounced at lower quantities of agonist doses. In order to rule out the plausibility that the measured parameters were caused by the release of ADP or TxA2, Rg1 was further evaluated in conjunction with Apyrase and indomethacin. It was discovered that the cocktail significantly reduced thrombin-at 0.1 U/mL-influenced thrombocytes, which demonstrated Rg1 actions exclusive of TxA2 and ADP. Rg1 demonstrated synergistic suppression of platelet aggregation when combined with an antithrombotic compound, salvianolic acid A. Rg1 has also been shown to inhibit collagen, fibrinogen adherence and subsequent adhesion, clot retraction, and the activation of PKC (protein kinase-C) Akt and ERK (Fig. 5). Rg1 at an oral dosage of 10 mg/kg had significant inhibitory influence on arterial occlusion duration whilst the latter was approximately 46% longer compared to that of the baseline control in an arterial thrombosis model, in vivo.

4.2. Ginsenoside, G-Rg3

One of the ginsenosides that is commonly researched, G-Rg3, offers a wide range of therapeutic efficacies, notably for treating CVDs. Owing to diverse pharmacological mechanisms, appraisals have demonstrated that G-Rg3 has a number of Cardioprotective and antithrombotic actions. In the past, researchers have demonstrated that Rg3 reduced rat thrombocytic aggregation caused by thrombin as well as collagen at concentrations of 0.1 U/mL as well that of 2.5 μg/mL, respectively, in a dose-dependent manner (Lee et al., 2008).

Kwon (Kwon, 2018a, b) contemporarily has looked into other mechanisms behind the impact of Rg3s' anticoagulative activity on human thrombocytes. Rg3 at an administrative concentration in midst of 50-300 μM, significantly reduced the amount of Ca2+ inflow, [Ca2+]i (Intracellular Ca2+), and thrombin-incurred platelet agglutination in dose related manner.

However, the results of the study explicitly demonstrated that Rg3 hindered and reduced [Ca2+]]i levels and Ca2+ influx by the process of phosphorylating ERK and inositol 1,d4,5-triphosphate receptor protein I in a cAMP-dependent manner, as demonstrated through the finding that the A-kinase antagonist (Rp-8-Br-cAMPS) increased [Ca2+]i, dose dependently, whist there was no discernible distinction when the thrombocytes were developed in confluence to the Rp-8-Br-cGMPS. The down regulation of intracellular Ca2+ concentrations inhibited the granular discharge as well, particularly the surface expression, of a granulation marker, commonly called as P-selectin. Additionally, Rg3 increased cAMP levels however, also improved $VASP^{ser157}$ phosphorylation and in culmination the Rg3 conserved its ability to significantly dose-dependently block clot retraction and bind fibrinogen in combination to fibronectin adhesion to integrin $\alpha_{IIb}\beta_3$ **(Fig. 5**).

4.3. G-Rg5 and G-Rg6

When Rg5's counter-thrombotic activity was evaluated versus the ADP (4 μM), collagen (1 μg/mL), AA (50 μM) and U46619 (4 μM), it was discovered that it was efficient against the induction of rat platelet aggregation by collagen, U46619 and AA with corresponding IC50 values of 409 μM, 102 μM and 8 μM (Lee et al., 2009). Similar to this, Rg6's IC50 values of 76 μM and 286 μM, in rodent thrombocyte aggregation mode, induced by AA- and U46619, were proven efficacious (Lee et al., 2010). But it's important to investigate how they work to inhibit the aforementioned needs to further determined.

4.4. Ginsenosides, G-Rh1, 2 and 4

In rat platelets activated by collagen and ADP, G-Rh1 and G-Rh2 were investigated because they potentially flaunted anticoagulant properties. Rh1 (administered at a concentration of 1 mM) had a minor antiplatelet effect by slightly inhibiting platelet activation and by lengthening the duration it took for fibrinogen to clot in response to thrombin (Matsuda et al., 1986) . Eventually, in regards to G-Rh1 and 2, Shin et al (Shin et al., 2015) investigated the impacts on thrombin incurred human platelet agglomeration and found no evidence of an inhibitory impact at the tested dose. Bearing an IC50 of 200 μM and then 119 μM, respectively, Rh4 was evidenced to be more potent than acetylsalicylic acid (ASA), which inherently bore an IC_{50} of 63 μM and 468 μM, respectively, against U46619 in combination to AA influenced rat thrombocyte aggregation (Lee et al., 2010).

4.5. Ginsenosides, G-Rs3-5

According to Lee et al. (Lee et al., 2009), G-Rs3 to 5 demonstrated modest antiplatelet effects in confrontation to U46619 at 4 μM, collagen at 1 μg /mL and AA at 50 μM,. These ginsenosides appear to be ineffective antithrombotic agents, according to the results.

4.6. Ginsenosides, G-Rk1 and 3

Lee et al. (Lee et al., 2009; Lee et al., 2010) observed that Rk1 had in the midst of 8-22 times higher anti-thrombotic impacts vis a vis ASA over collagen, at 4 μg /mL, ADP at 4 μM, U46619 administered at 4 μM with a threshold baseline of collagen at 1 μg /mL in amalgamation to AA at 50 μM. Eliciting an an IC50 of 192, 187, and 128 μM, in a respective manner. Rk3, likewise demonstrated higher antithrombotic effects in confrontation with ASA against U46619 at 4 μM, collagen at 4 μg/mL. The antiplatelet activities pertaining to Rk1 were later discovered by yet another investigation, which also thoroughly examined its molecular features (Ju et al., 2012). Rat thrombocytic agglomeration caused by collagen at 1 mg/mL whilst, +-AA at 3 μM was inhibited by Rk1 (keeping concentration in the midst of 10-50 μM in a dose-dependent fashion. The research showed that Rk1 lowered 12-hydroxy-5, 8, 10, 14 -eicosatetraenoic acid, one of the AA metabolites, as well as thromboxane B2 (TxB2) formation via inhibiting COX (**Fig. 5**). With Rk1 therapy, intracellular calcium concentrations dropped. Attributing to the translocation of 12-LOX from the cytosol to the plasma membrane is linked to calcium levels intracellularly. Likewise, it has further been suggested that owing to trans-location of 12-LOX arising from plunged level of Ca2+. This mechanism was behind a deescalated level of Eicosatetraenoic acid level whereas, the letter was antagonized by G-RK1. The research demonstrated the possibility of using metabolomics to investigate antiplatelet medications, and Rk1 emerged as a strong candidate for thrombocytes linked to CVDs.

4.7. Oleanane-type G-Ro regulates human thrombocytes functions

It has been noted that G-Ro, at a dose of 1 mg/mL, inhibits the emission of ATP from rabbit thrombocytes that have been stimulated by

collagen at a dose concentration of 10 μg/mL, AA (100 μM, ADP (20 μM),) and platelet-activating factor (PAF) (2 ng/mL) (Teng et al., 1989). In their study of the antagonistic effect of Ro (from 50 to 300 μM) on human thrombocytes activated by thrombin protein at a concentration of 0.05 U/mL, Kwon et al. (Kwon et al., 2015), discovered a suppression of platelet agglomeration, in a dose dependent manner, with an IC_{50} of 155 μM. The usage of kinase inhibitors, specifically Rp-8-Br-cAMPS and eventually the increased, Ser1756, phosphorylation of inositol 1,4,5-triphosphate receptor-I, which prevents $[Ca^{2+}]i$ mobilization and subsequently prevents thrombocyte aggregation, show that Ro significantly suppressed Ca2+ concentrations in a cAMP-contingent upon way. Ro was shown to have broad-spectrum counter-thrombotic effects, which in turn escalated cAMP levels, hindered $[Ca^{2+}]i$, ATP, 5-HT emission, and P-selectin expression (Fig. 5). Remarkably, the usage of Rp-8-Br-cAMPS revealed that the majority of the circuits were centered on cAMP.

Shin et al. (Shin et al., 2016) revealed antithrombotic and counter-adhesive activities of ginsenoside Ro and demonstrated that it prevented thrombin incurred human thrombocyte aggregation, in a dose dependent fashion, via the elevation of cAMP-dependent $VASP^{ser157}$ and the robust abolishment of clot aggregation via inhibiting glycoprotein IIb/IIIa ($\alpha_{IIb}\beta_3$) (**Fig. 5**). Ro inhibits clot retraction, owing to contraction of fribrin-mesh, and the binding of sticky ligands fibronectin and fibrinogen to integrin $\alpha_{IIb}\beta_3$ via down-regulating the PI3K/Akt cascade, according to Kwon's later findings (Kwon, 2019).

The antiplatelet properties of Ro were recently studied by Shin et al (Shin et al., 2019) on thrombin mediated human platelets, and they discovered that Ro (in midst of 50 to 300 μM) greatly prevented thrombocyte aggregation. Vasoconstriction and thrombogenesis were caused by TxA2 production, which Ro significantly reduced by blocking AA discharge in a dose-dependent pattern. The development of thrombus is started by the production of TxA2 via AA, that itself is made by COX-1 in addition to thromboxane-A synthase (TxAS) (Jennings, 2009; Ruggeri, 1997). The synthesis of TxA2 is recognized to be induced by phosphate activated MAPK (p38-MAPK and ERK2), and AA release is eventually caused by the stimulation of cytosolic phospholipase A2a (cPLA2a) (Irfan et al., 2020; Kudo and Murakami, 2002). All of the aforesaid factors that contribute to the synthesis of TxA2 have, dosage dependently, been decreased by Ro administration (**Fig. 5**). The introduction of SB203580 provided conclusive proof that the Ca2+-dependent phosphorylation of cPLA2a by p38MAPK was constituted as the cause of AA and TXB2 suppression (p38MAPK antagonist). Conclusively, G-Ro have a propensity strong option for preventative therapy against thrombotic CVD.

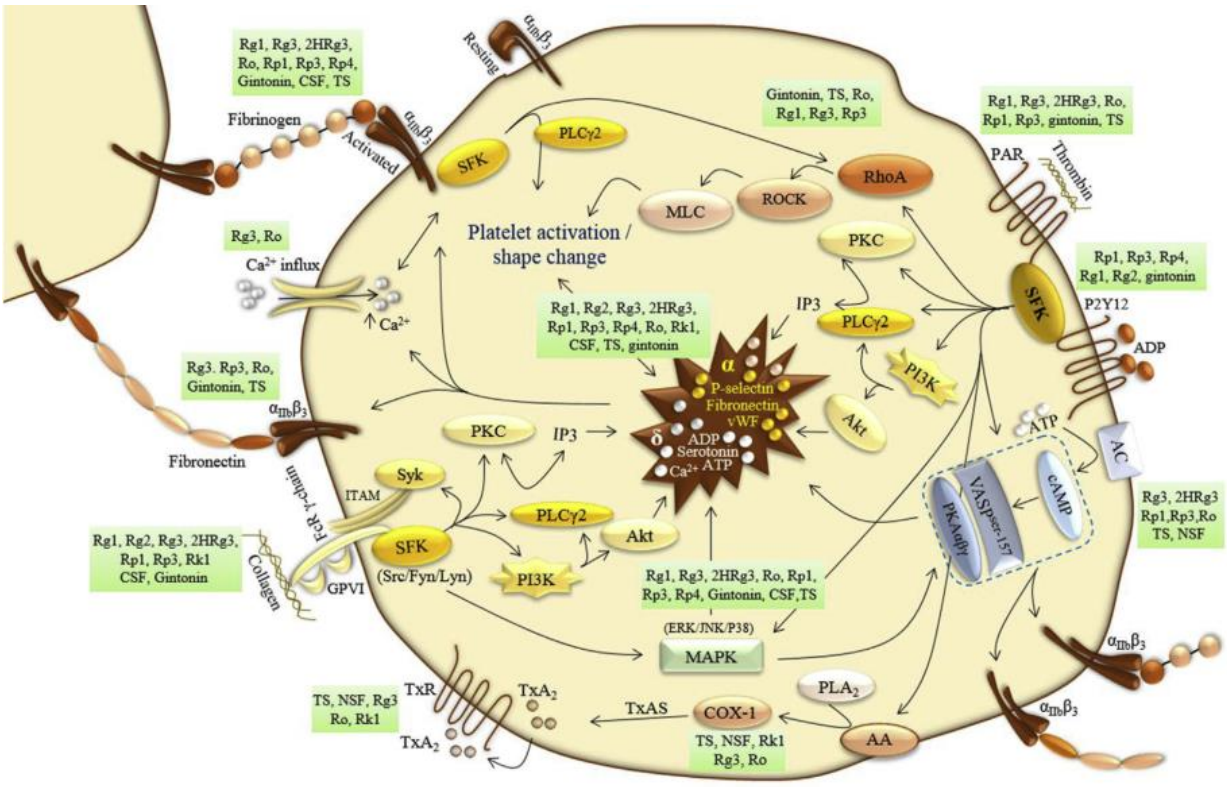


Figure 5: depicts the mechanistic cascade of platelet activation and the impact of multifarious ginsenosides on the homeostasis and regulation of thrombocytic activities that influence specific sensory-proteins or downstream signaling processes (Irfan et al., 2020).

AC-adenylyl cyclase, AA-arachidonic acid, **Akt**-protein kinase B, **CSF**-crude saponin fraction, **COX**-cyclooxygenase, **MAPK**-mitogen-activated protein kinase, **IP3**-inositol-1,4,5- triphosphate, **PAR**-proteinase-activated receptor, **MLC**-myosin light chain, **PKC**-protein kinase C, **PLA2**-phospholipase A2, **PLCg2**-phospholipase C gamma-2, **PKA**- protein kinase A, **SFK**-Src family kinase, **TS**-total saponin, **VASP**-vasodilator-stimulated phosphoprotein, **ROCK**-Rho-associated protein kinase, **TxA2**-thromboxane A2, **TxAS**-thromboxane synthase, **vWF**-von Willebrand factor.

5. CONCLUSIONS

Above arguments are based on the cogency of ginsenosides as an antiplatelet compound. Ginsenosides, Rg1 and Rg2, deter the aggregation of thrombocytes, collagen and fibrinogen at molecular level in addition to inhibiting the thrombin incurred thrombopoiesis. Moreover, the Rg3 significantly attenuates the Ca2+ influx, Intracellular Ca2+, and thrombin contracted platelet agglutination. Similarly, Rg5 and Rg6, have the ability to deregulate the expression of Arachidonic acid and consequent TxA2 and PGs. Whereas, Ginsenosides, GRh , GRk and GRs series, employ the same mechanism with the added U46619 modulation. Yet, the Oleanane-type Ginsenoside Ro, restricts the expression of glycoprotein IIb/IIIa ($\alpha_{IIb}\beta_3$) and the competitively binds to the sticky ligands fibronectin and fibrinogenin confluence to integrin $\alpha_{IIb}\beta_3$ eventuating in desensitization of the PI3K/Akt pathway. In culmination, these antiplatelet manifestations of the ginsenosides can come in handy when dealing with disorders such as CVD, Hyperlipidemia and COVID-19.

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