Advancement in cytoprotection through suppression of p53 protein

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ABSTRACT

P53 proteins are the one the most important tumor suppressors which helps in modulating the fate and determination in relative for a variety of cellular regulations via cell apoptosis. Here the p53 suppression in the main protein which helps in cytoprotection, neuroprotection, hepatoprotection and radioprotection like actions which may be natural like curcumin, Bilobalide, silymarin, Andrographolide etc. whereas, synthetic suppressor of p53 protein are pifithrin-alfa, pifithrin-mu, amifostine, 8-hydroxyquinoline, salidroside etc. In cytoprotectives the cellular targeting would induce the p53 tumor suppressor which induces differentiating cells restriction or cell death. The neuroprotective agents act via neuro inflammation, oxidative stress, autophagy, reactive oxygen units, and cell death signal cascade, which will occur instant when cell proliferationis acute, pro-apoptotic factors like Bax, caspase-3, Nuclear regions and p53; initiates the mechanism of neuronal apoptosis. The radioprotection and hepatoprotection occurs via the mechanism of down-regulating pro apoptotic factors like; Alpaf 1, Noxa and Bax., where in hepatoprotection the livers cell death and rupture, p53-down regulated the liver lethality, and therefore p53 is a protective agent that would protect hepatic rupture via apoptosis. The recent advancements via p53 suppression leading to various apoptotic factors is a great discovery for the various cytoprotectives, radioprotective, hepatoprotective and neuroprotection actions.

Keywords: p53 protein suppression, Natural Products, Apoptosis, Down-regulation, Radioprotection, Hepatoprotection, Neuroprotection, Cytoprotection.

1. INTRODUCTION

P53 protein has been found to involved in cytotoxic effect of various therapeutic agents and radiation. Activation of p53 protein by cytotoxic agents results in induction of apoptotic cell death via proteolysis. Thus, temporary suppression of p53 protein by small molecules protects cell from variety of cytotoxic agents. Examples of suppressor of p53 protein are pifithrin-alfa, pifithrin-mu, amifostine, 8-hydroxyquinoline, salidroside etc.

The present work focuses on review of various cytoprotective which regulate the activity of p53 protein through different mechanism. Moreover, it includes the area of possible application of these agents in the disorder associated with over-activation of p53.

P53 is an important in pain responses, majorly in activating by stopping cell cycle or apoptosis with acute DNA proliferations [1][57][58]. In standard cells the level of p53 is very low. DNA proliferation and other distress may

activate p53 protein to perform some of its main role like cell growth stoppage, DNA rupture and cell death. Hence, apoptosis is the final options in order to stop proliferation of the cells.

2. ROLE OF p53 IN CYTOPROTECTION

The exposure to cellular targeting would induce the p53 suppressor, a transcriptional factor, to induce cell death [2][59][60]. The selection of this cell activity can be affected by many proteins, inhibitors, and the activity of p53 suppressors. P53 acts through two main apoptotic pathways. The extrinsic pathway, apoptotic receptor will start the initiation of a caspase –cascade factor, whereas the intrinsic pathway; this transfers the Bcl-2 factor towards the pro-apoptotic form, and encourages for developing of apoptosome, and hence leads to caspase-mediated apoptosis. The majority of cell death is mediated via p53 mediated mechanism. Hence, using of the apoptotic functions of p53 can leads to cytoprotection by suppressing p53 proteins [3][61][62].

Radioprotection from cytotoxic effects of radiation

The apoptotic pathways responsible for cell damage has identified the process that occur due to delayed in radiological damage and these process acts as a potent aim for delayed irradiation intrusion [4]. The ATM/ATR, p53mediated proteins regulates the DNA proliferative apoptotic pathways. ATM/ATR acted as a main role in triggering programmed cell death by down-regulating pro-apoptotic factors like; Alpaf-1, Noxa and Bax. Example of p53 suppressing via radioprotection in IR induced apoptosis was pifithrin-μ, Amifostine, β-glucagon have shown radioprotective activity [5]. Similarly, the over expression of Bcl2, a negative regulator of pro-apoptoticfactors, has shown to effectively increase the potency of radiated cells of hematopoietin. Hence, radioprotection can be achieved by suppressing molecular targeting of p53 proteins.

3. ROLE OF p53 in IN NEUROPROTECTION AND HEPATOPROTECTION

Neuroprotective activity of p53 can be seen in the case of Traumatic brain injury via suppressing neuro inflammation, oxidative stress, autophagy and apoptosis [6][63][64][65]. The TBF positively shows that improper regulation of dopamine and reductions in tyrosine hydroxylase activity is the main reason for this traumatic brain injury via p53 mediated apoptosis [66]. The delayed effect in traumatic brain injury includes generation of neuronal swellings, reactive oxygen species, and programmed cell death causing cascades affecting the TBFs. When cell damage is acute, apoptotic factors like Bax, caspase 3, transcription nuclear regions of p53 mediated protein, begins the process of neuronal death. p53 gene, important for expressing activated genes initiated the cell apoptosis in relate to various cell distress. It is seen that p53 mediated apoptosis plays a major role in the growth of hypo ischemic brain cell apoptosis [7]. The activation of JNK signaling has appeared to regulate neuronal damage after TBI which is also a p53 mediated mechanism leading to apoptosis hence; p53 down regulator of JNK pathway is important for Neuroprotective action for various naturally and synthetically p53 mediated suppressing action [8].

The mammalian target of rapamycin (mTOR) receptor and its down regulation is also important for cascade mediated apoptotic pathway like, Beclin 1 and light chain 3 [9][67]. The autophagic and anti-apoptotic proteins

(e.g.Bcl 2 and Bcl XL) can attach with Beclin1 and decrease the p53 activity. Hence, interactions between anti-apoptotic and autophagic proteins play crucial role in cyto- protection and neuroprotection [68].

Example; Pifithrin alpha, p53 suppressor protein, was discovered to prevent neuron death by suppressing p53 transcriptional activity, caspase activation, and mitochondrial dysfunction [10]. Pifithrin-α has illustrated and be effective in preventing neuronal apoptosis in ischemia and various neurodegenerative disease. Hence, suppression of p53 is for determination of p53-dependent cascades and can be used in neuroprotection via various therapeutic techniques [11].

4. P53 SUPPRESSING AGENTS

1. Natural Origin
2. Synthetic Origin

Table 1: Natural Origin p53 Suppressing Agents.

S.No.	AGENTS	SOURCE	CONCENTRATION	MECHANISM	REFERENCE
1	Bilobalide	*Ginkgo biloba*	40 mg/kg	The neuroprotective mechanism of bilobalide is the beta Amyloid has used for reducing cellular toxicity regulates the free radicals and minimizes mitochondrial dysfunctioning by down regulating p53, activate JNK and ERK factors, hence prevent neuronal death.	[12] [13]
2.	DTAS (Diallyl trisulfide)	*Allium sativum* (garlic)	1000 mg/kg	Acting as a hepatoprotective agent via down regulating cell apoptosis via stopping S phase eventually leading to p53 suppression so that Bax, p53, and cytochrome C and reduce the activity of Bcl2 gene and leading to apoptosis.	[14]

3.	Glycyrrhizic acid	*Glycyrrhiza glabra* (Liquorice)	15 mg/kg	P53 can lead to apoptosis majorly through p53 suppressing genes such as PUMA, NOXA and Bax.	[15] [16]
4.	Schisantherin A	*Schisandra sphenanthera* (Five-flavor berry)	700 mg/kg.	P53 mediated pathway negatively regulates pregnane-X receptor activity, indicating that wuzhi activates Pregnane X receptor via inhibition of the p53 pathway.	[17]
5.	Resveratrol	*Citrus aurantium* L. (Zhi-shi)	6mg/kg	Zhi-shi blocked apoptosis by p53 down-regulated apoptosis regulator PUMA, AMPK-SIRT and JNK pathways.	[18]
6.	Curcumin	Curcuma longa	50mg/kg	Apoptosis can be reduced via p53 suppression through the initiation of caspase cascade regulation. Where, independent type mechanism occurs when p53 induces the transcription of a gene encoding protein such as the Fas which is essential to promote apoptosis. On the other side, the dependent type mechanism involves when p53 initiates Bax factors.	[19] [20]

7.	Catechin	*Anacardium occidentale*	100mg/kg	P53, Bax and Bcl-2 are major genes which controls the apoptosis. Mechanisms by involving theBcl2, Baxand activation of caspases which induces apoptosis and catechin caused the down regulation of those p53 mediated proteins.	[21]
8.	Silymarin	*Silybum marianum*	200mg/kg	Silymarin has shown the p53 suppressing activity by down regulating the production of apoptotic proteins, p53 mediated apaf 1, and reduced caspase 9 activitieswhich leads to apoptosis and hence acts as neuroprotective for Cerebral ischemia.	[22]
9.	Chlorogenic acid	*Phyllostachys edulis*	30 mg/kg	Chlorogenic acid has shown suppressing activity on apoptosis and autophagy by suppressing expression of p53 and caspase-3.	[23]
10.	Andrgrapholide	*Andrographis paniculata*	0.1 mg/kg	Andrographolide reduce vascular smooth muscle cells apoptosis via p38 related p53 suppression and Bax. Hence acts as neuroprotective action.	[24] [25]
11.	Rutin	*Ruta graveolens*	30mg/kg	Rutin inhibits apoptosis via decreasing Bcl2 and	[26]

				increasing P53 suppressor gene, regulates the cell cycle.	

4.1 BILOBALIDE

The tree of Ginkgo has been obtained from *Ginkgo biloba*; hence considered as a living fossil. The concentrated and pure extracts of Ginkgo leaf initiate protection from neuronal and vascular injury [13]. P53 initiates apoptosis via molecular mechanisms leading to the activation of Bax, Fas as direct involvement, leading to release of cyt.c and caspase activation. The extract of Ginkgo biloba stops cell apoptosis, mediated by p53 suppression, where the biloba extract improves the p53 mediated protein strands of mRNA and involves the Bcl2 protein to decrease the release of cytochrome-c to cellular space, and inhibits caspases activation [27][69][70]. Ginkgo leaves was used in traditional medicine system for improving memory and age-related deterioration which provide neuroprotective action [12].

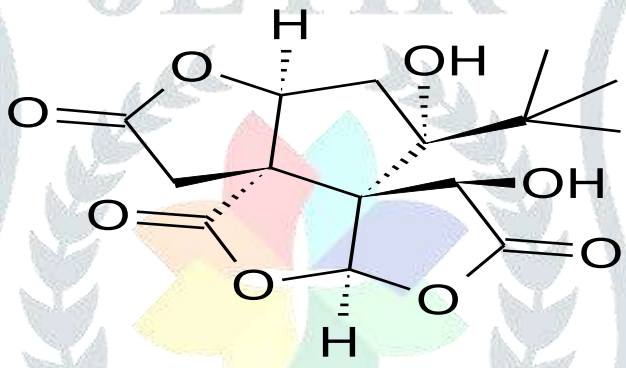

Fig.1: Structure of bilobalide and neuroprotective mechanism of action.

The neuroprotective mechanism of bilobalide can be achieved by the beta Amyloid cascade p53 mediated mechanism or p53 suppression which was used for reducing cellular toxicity via regulating the free radicals and minimizes mitochondrial dysfunctioning by down regulating p53, which will activate JNK and ERK factors which suppresses Bax and Fas leading to inhibit the release of cyt.c and caspases hence, prevent neuronal death [13] [28]. Bilobalide has a strong defensive effect on brain cells for example neurons and Schwann cells. Bilobalide has also shown to decrease the activity of p53, Bax, and caspase-3 proteins and also inhibit ROS-induced cell death in PC12 cells [29][71]. Bilobalide also affects neurogenesis and synaptogenesis by increasing the levels of transcription factors. Hence, this is clear that Bilobalide is acting as neuroprotective agent by suppressing the p53 into the brain cells. *Ginkgo biloba* extract was useful in treatment of neurodegenerative disease and in the early stages of Alzheimer's disease [12][30].

4.2 DIALLYL TRISULFIDE (DTAS)

Garlic is a natural product which is obtained from *Alium sativum*, considered common spice and also as a good herbal remedy having good health benefits as it boosts the immunity. It is an antibacterial, antifungal, antioxidant, anticancer, and antiviral agent. Also, it is being used as the platelet aggregator and having an antihypertensive property. The main active chemical constituents of garlic are diallyl thiosulfonate (allicin), diallyl sulfide, diallyl disulfide, diallyl trisulfide, ajoene, S allyl cysteine, and S allyl cysteine sulfoxide (alliin) [31]. A recent study tells that garlic is acting as a hepatoprotective agent and the Diallyl trisulfate is the chemical which is responsible for this [14].

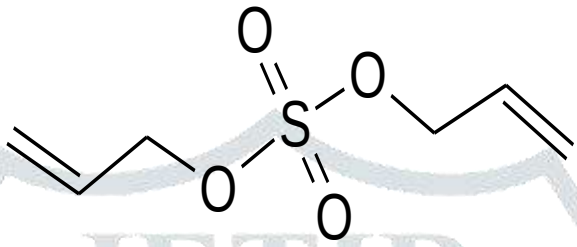

Fig.2: Diallyl trisulfate and cytoprotectives mechanism of action.

The p53 mediated protein will cause cell division stops the cell cycle and induces apoptosis. The diallyl trisulfide will cluster up the bax, p53, cyt.c which will help and will reduce the potency of bcl-2 which is main reason for p53 mediated apoptosis leads to suppressing the p53 protein activity [32]. Cytoprotective mechanisms of allium species will look for electrophiles will reduce cell multiplication and reactive oxygen species; which induce cell apoptosis by DNA injury. [33].

4.3 GLYCYRRHIZIC ACID

Glycyrrhizic acid is a natural and major pentacyclic triterpenoid glycoside obtained from dried and unpeeled roots and stolons of *Glycyrrhiza glabra* of family Leguminosae. Glycyrrhizic acid is a potent anti-inflammatory, resistant to viral attack up-to a degree, and also possesses carcinogenic activity, etc. Recent studies shown the chemo-preventive action of glycyrrhizic acid was observed for 1, 2-dimethyhydrazine causing tumor via apoptosis [16].The chemical constituents of liquorice are terpenoid saponin glycyrrhizin/ glycyrrhizic acid is present in 6-14 %, glucose, sucrose, glycyramarin and asparragin (2-4%) giving it bitter taste.

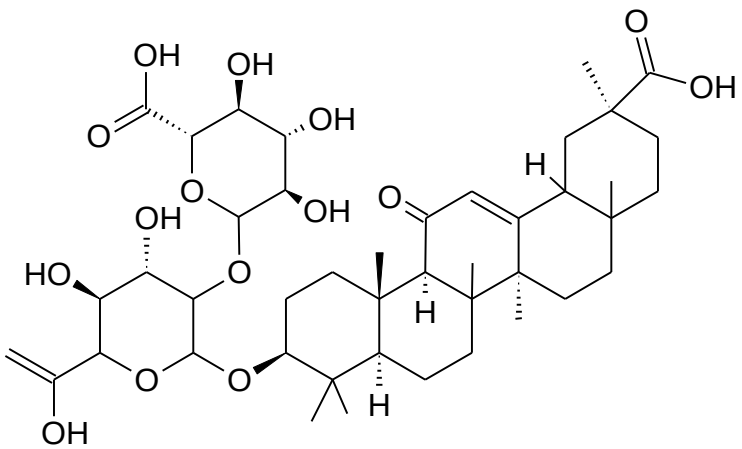

Fig.3: Glycyrrhizic acid and its hepatoprotective mechanism of action.

The p53 may induce to cell death for most of the part through p53 mediated genes like P21, PUMA, NOXA and Bax. Bax, which areup regulators and the antiapoptotic protein Bcl-XL, was a down regulator which mediates the release of cyt.c from mitochondria to cytoplasm. The appearance of Bax protein is a direct conclusion of the release of cyt.c via mitochondria and activates the caspase 9 and here the glycyrrhizic acid plays a mojor role of suppressing those Bax genes via inducing Bcl-XL a downregulator of p53 mediated apoptosis [34][72][73][74]. Also, glycyrrhizic acid induces the Inhibitory apoptotic proteins (IAPs), control cell death via various means that play a major role in suppression of the apoptosis. Caspase-IAP1and c-IAP2, as the main body of IAPs, could suppress the activity of caspase 3, 7; which can lead to cell death. When cell death begins from that second's mitochondria derived activator of caspases, which was released by mitochondria into the cytoplasm, binds and inhibits IAPs; hence, decrease the caspases via IAPs results in suppressing the cell death. Therefore, Glycyrrhizic acid acts as suppressing p53 dependent hepatic apoptosis leads to hepatoprotection [15][75].

4.4 SCHISANTHERIN –A

Schisantherin-A is obtained from dried fruit of *Schisandra sphenanthera* (Five-flavor berry). The Wuzhi tablet was containing 7.5 mg schisantherin- A contents per tablet, was prepared by the ethanolic extract of *Schisandra sphenanthera* which is mentioned during hepatic damaging [35]. P53 and p21 levels were explored whether wuzhi can block p53/p21 signaling to promote liver repair hepatotoxicity.

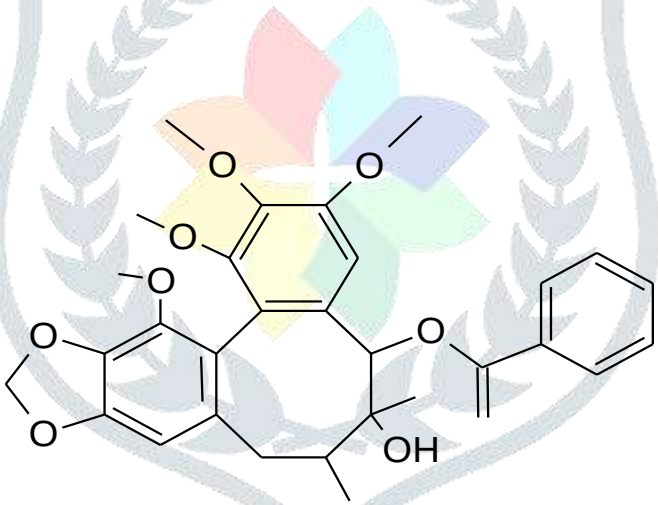

Fig. 4: Schisantherin A and hepatoprotective mechanism of action.

Wuzhi has shown an important down regulation of p53 or p21 utterence, with introducing cell cycle related proteins like cyclin D1 and multiplying cell nuclear antigens [17]. Which tells the important role of Pregnane x receptor in liver regeneration [36]. Thus, p53 pathway negatively controls the pregnane X receptor action, indicating that wuzhi can activate Pregnane X receptor via inhibition of the p53/p21 pathway and hence leading this hepatoprotection becauseof initiated the pregnane x receptor pathway and reduces liver damage and acting as hepatoprotective agent [37].

4.5. RESVERATROL

Resveratrol was a phenolic compound found in *Citrus aurantium L*. (Zhi-shi) citrus fruits and vegetables. It possesses various medicinal activities like cure ageing, prevents cancer, prevents inflammation and also prevent from cardiovascular diseases. A main role of resveratrol is in oxidative stress, apoptosis, mitochondria functional and angiogenic signaling pathways, via reducing cell death through the SIRT1 pathway [38]. This is the reason for choosing resveratrol in control for liver damage which is due to oxidative stress. The liver metabolism could be used to check the effect of Zhishi on liver lipid metabolism disorders caused due to overdosing of Acetaminophen at systemic level and to determine main target related to hepatic toxicity. Then the p53 suppressive pathway was deployed to explore the effect of Zhishi on hepatic apoptosis induced by Acetaminophen [18].

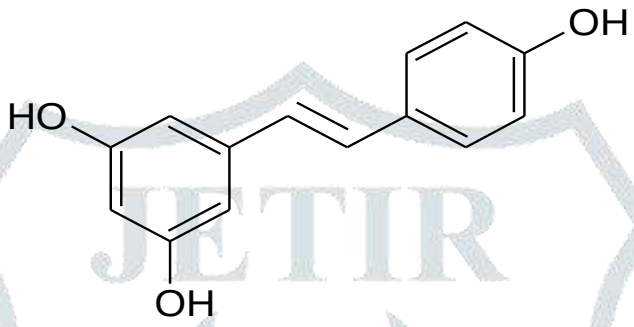

Fig.5: Resveratrol and its hepatoprotective mechanism of action.

P53 protein is a cell transcriptive factor which activates genes participated in programmed cell death event which can affect cell death via reaction with Bax. Hence, programmed cell death can be affected via caspase-9 activation which is induced by Bax (a p53 mediated protein) which can also assist in Acetaminophen-mediated hepatocyte apoptosis [39]. The m-RNA expressing the pro-apoptotic factors like Bax and Caspase3 has induced simultaneous up regulation in cells which causes apoptosis of the cell was treated with the Zhishi or Resveratrol. Hence, the protein levels of BAX and Caspase3 in BRL-3A cells which was down regulated by Resveratrol of these pro-apoptotic genes after showing therapeutic action by suppressing those Bax and Caspase 3,9 activities [40][76]. Finally, these mechanisms conclude that Zhishi prevents hepatocyte apoptosis caused by Acetaminophen via down regulating p53 suppressive hepatocyte leads to apoptosis and used as hepatoprotective agent.

4.6. CURCUMIN

Curcumin was flavonoids which arehaving a yellow color pigment which was obtained from the rhizome of the *Curcuma longa*, commonly called as turmeric, belongs to the family of Zingiberaceae and a native of south and southeastern Asia, particularly in India [41]. Turmeric possesses flavoring effect, coloring property, and also used as additive. The most important chemical constituent of turmeric are polyphenolic compounds called curcuminoids, which is having curcumin, demethoxycurcumin, and bisdemethoxycurcumin. The cuercumin is acting as hepatoprotective, neuroprotective and preventing cell death acting on the p53 supressing pathway. With the very less adverse action it is effectively acting as the nobel compound for acting as p53 regulator via cytoprotection [42][77].

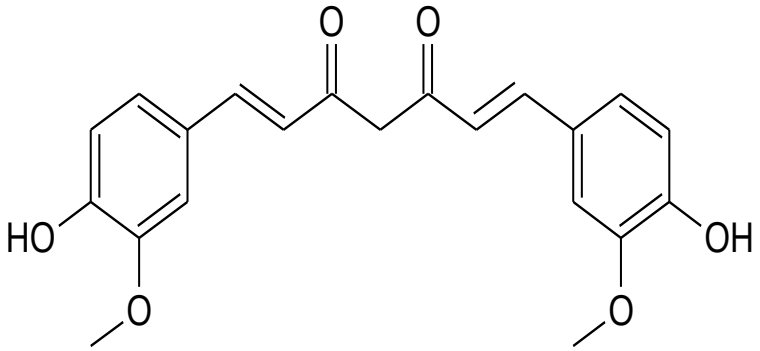

Fig.6: Curcumin and its cytoprotective mechanism of action.

Apoptosis can be cause by p53 mediated protein by initiating the caspase- cascade regulation. Where, independent type mechanism occurs when p53 induces the transcription of a gene encoding protein such as the Fas which is essential to promote apoptosis. On the other side, the dependent type mechanism involves when p53 initiates Bax factor [20].

Curcumin helps in P53 suppressing cellular proliferation via two mechanisms. In general, within the fibroblastic cells, p53 initiates G1 phase blockage in response to DNA rupture, which was essential for the cells to repair their previous function before initiating the cell cycle and curcumin didn't allow p53 protein for its action on G1 phase hence, apoptosis is delayed [43]. In abnormal differentiating cells or radiated thymocytes, triggering p53 shows programmed cell death or apoptosis. Therefore, the control and expression of p53 gene is important for the initiation of apoptosis inthe cancerous cells which is effaceable as cytopreventive and chemotherapeutic agents [19].

Curcumin stops cell death via the down regulation of p53 protein and targets of p53 cyclin dependent kinase interacting protein and growth depletion; DNA damaging proteins; and curcumin interact with cell cycle, or other apoptotic mediated proteins like, Bcl-2 or Bax and didn't allow p53 to cause apoptosis in the cells which is leading to cytoprotection [44].

4.7. CATECHINS

Catechins are substances obtained from *Anacardium occidentale,* that possesses neuroprotection and hepatoprotection by various mechanisms at the cellular level, affecting various intra cellular inducing pathways, and modulating gene expression and protein functioning of p53 [21].

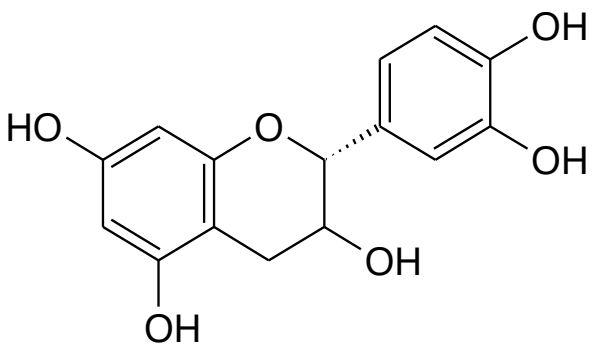

Fig.7: Catechin and its hepatoprotective mechanism of action.

The action of catechin against induced hepatotoxicity is because of very main genes like p53, Bax and Bcl-2 which is involved in apoptotic process [45]. The Bcl-2 is an inducer of apostosis, and its down regulation will reduce cellular toxicity. Where, Bax also promotes apoptosis via mediating p53 protein. Catechin prevented the up regulation of Bax by p53 supression, thus acting as the hepatoprotective agent [46]. Where p53 induced apoptosis involved various mechanisms involving the Bcl2, Bax and activation of caspases which induces apoptosis and catechin caused the down regulation of p53 protein via which it acts as a hepatoprotective agent [21].

4.8. SILYMARIN

Silymarin is the chemical constituent of plant *Silybum marianum*. It is considered as a potent kind of drug for all kinds of liver diseases like cirrhosis, viral hepatitis, and several other liver diseases. Silymarin is considered as a neuroprotective as well as hepatoprotective agent [22].

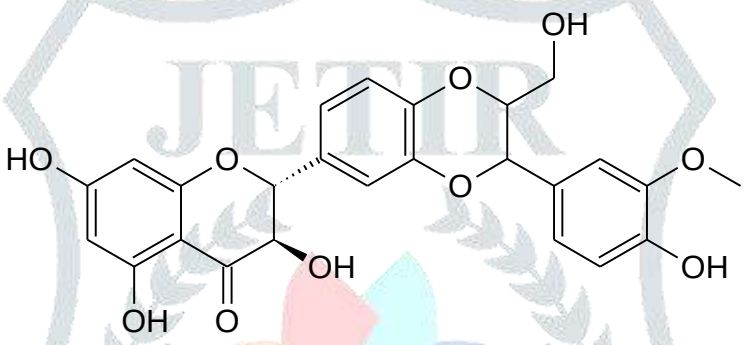

Fig.8: Silymarin and its neuroprotective mechanism of action.

Neuroprotective pathways of Silymarin in cerebral ischemia can be done via 3 main mechanisms; inflammation pathway, oxidative pathway, apoptotic pathway. Inflammatory pathway: It is done via inhibiting the activation of NF-kB based generation of cyclooxygenase-2 (COX-2) and nitric oxide. Hence, by regulating NF-kB would decrease both oxidative stress as well as nitrosative stress via down regulating the generation of Reactive oxygen species (ROS) and Nitric oxide (NO), which leads to neuronal death [47].

Oxidative pathway: It is done via the help of silymarin as it reduces the formation of free radicals mediated protein and lipid oxidation, which is having a power to reducing state and leads to oxidative stress, further causing neuronal death [48].

Apoptotic pathway: Silymarin firstly acts on the mitochondria which are leading to p53 protein and cytochromes as it helps by preventing formation of the apoptosomes via suppressing the apoptotic protease activating factor-1 (apaf-1) which regulates the activation of caspases and leads to apoptosis and causing neuronal death and finally leading to neuroprotection [49].

Hence, silymarin has shown anti-apoptotic property by inhibition of the production of apoptotic proteins, p53 mediated apoptotic protease activating factor-1, and reduced caspase-9 activities which leads to reduced neuronal death and hence acts as neuroprotective for Cerebral ischemia.

4.9. CHLOROGENIC ACID

Chlorogenic acid has shown a positive regulation on apoptosis and autophagy by induced expression of p53 and caspase-3 [23]. For checking the effect of chlorogenic acid on apoptosis and autophagy, there is evaluation of p53 gene. The p53 gene controls the outcome of stressed cells by a cell cycle inhibition, which may allow repair the ruptured transcriptive units, or via removing these cells by promoting of cell death of these genes [50]. P53 also initiates an important role in autophagy as shown that p53 triggers cell self consuming factor in the hepatic toxicity [51]. Autophagy shows a stress process which avoids apoptosis, but also shows an more cell injury pathway and the Chlorogenic acid will directly suppress the p53 mediated proteins for Neuroprotection [52][78].

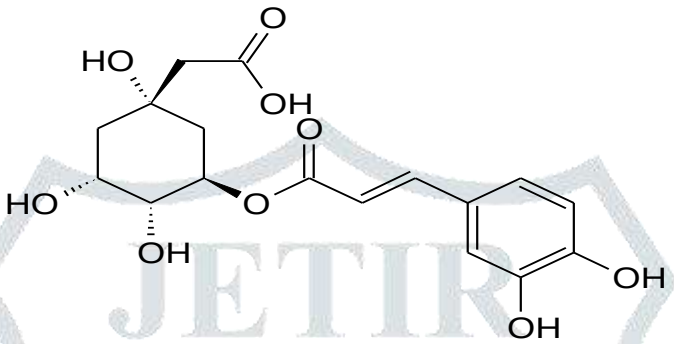

Fig. 9: Chlorogenic acid and its neuroprotective mechanism of action.

p53 and caspase-3 in the indicates the importance of caspase-dependent cell death and the Bax levels supported the pathophysiological role of this pro-apoptotic protein in nephrotoxicity and hence chlorogenic acid has suppressing activity on apoptosis and autophagy by suppressing p53 and caspase-3which is beneficial in the induced apoptosis and leading to neuroprotrective activity [53].

4.10. ANDROGRAPHOLIDE

Andrographolide is been isolated from stems and leaves of *Andrographis paniculata*having immunologic action, antibacterial property, protect from virus, anti-inflammatory, antithrombotic, and also hepatoprotective properties [54]. Andrographolide reduces vascular smooth muscle cells apoptosis via suppressing p38-mediated p53 supressor protein phosphorylation and Bax hence, Andrographolide stimulates vascular smooth muscle cells apoptosis which is beneficial for cerebral ischemia treatment as neuroprotective agent [25].

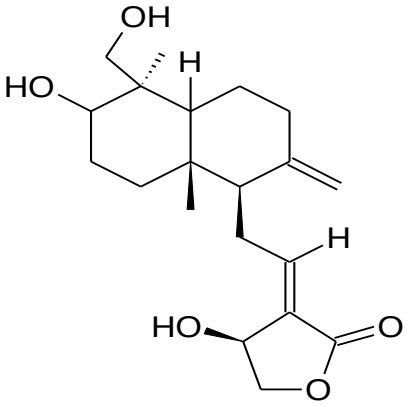

Fig. 10: Andrographolide and its neuroprotective mechanism of action.

The p38 mediated p53 suppressor phosphorylation and activation of caspase 3 was leading to subsequently activated the expression of Bax, the apoptotic protein which leads to vascular smooth muscle cell apoptosis causing neurotoxic action in cerebral ischemic cells and the andrographolide inhibits the caspase-3 activation, showing that andrographolide had reduced the action of programmed cell death which results in neuroprotective action of andrographolide [25][55][79][80].

4.11. RUTIN

Rutin is a flavonoids glycoside was obtained from *Ruta graveolens* which is possessing neuroprotection, anti-inflammatory, anti-carcinogenic, antiproliferative, and anti-oxidative stress effects via inhibiting the lipid peroxidation [56].

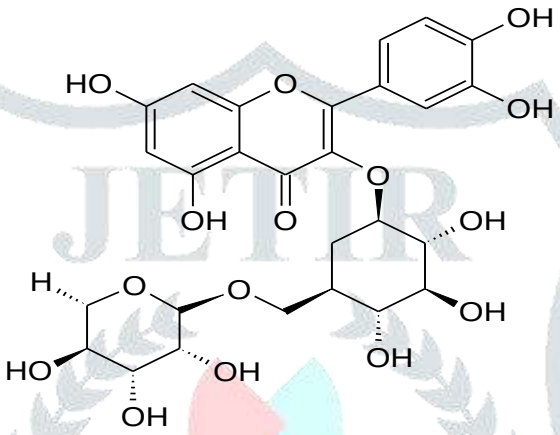

Fig. 11: Rutin and its neuroprotective mechanism of action via downregulating p53 gene.

Rutin mechanism is achieved via inhibiting cell death via decreasing Bcl-2 and increasing P53 suppressor proteins which regulates the cell cycle resulting cellular mechanism leading to reduce cell apoptosis via downregulation of p53 suppressor gene which binds to Bcl-2 and Bcl-XL. So, deactivating Bak and Bax apoptotic factors of p53 mediated proteins shows downregulation and has been acted as neuroprotective agent [26][81][82].

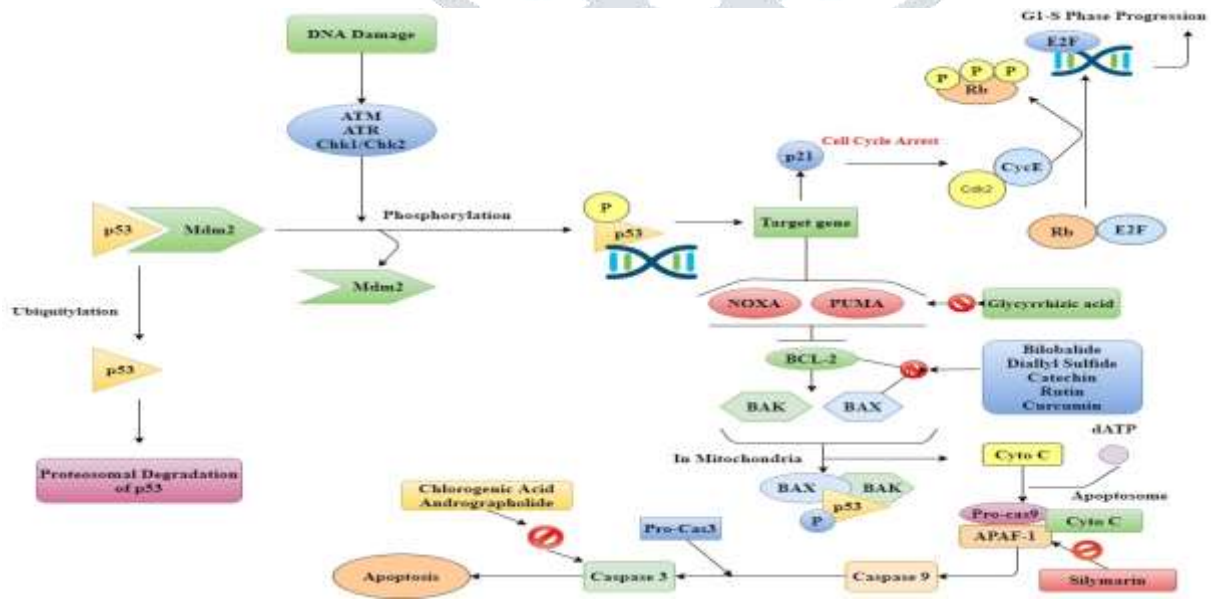

Fig. 12: Representative mechanistic pathway or interaction and role of p53 mediated proteins and the target site for inhibition of apoptosis by different molecules.

5 CONCLUSION

Here, we have discussed about the role of p53 in cytoprotection, hepatoprotection, neuroprotection and radioprotection of various natural products and their mechanisms. Here the p53 suppression in the main protein which helps in cytoprotection, neuroprotection, hepatoprotection and radioprotection like actions which may be natural like curcumin, Bilobalide, silymarin, Andrographolide etc. whereas, synthetic suppressor of p53 proteins include pifithrin-alfa, pifithrin-mu, amifostine, 8-hydroxyquinoline, salidroside etc. Firstly, we discussed about the natural p53 suppressor Bilobalide which is obtained from *Ginkgo biloba,* it needed in the concentration of about 40mg/kg showing the cytoprotectives activity acting as the protective agent where, the neuroprotective mechanism of bilobalide is the beta Amyloid has used for reducing cellular toxicity regulates the free radicals and minimize mitochondrial dysfunctioning by downregulating p53, activate JNK and ERK factors, hence prevent neuronal death. In case of DTAS (Diallyl trisulfide) obtained from garlic acting as a hepatoprotective agent via down regulating cell apoptosis via Stopping S phase eventually leading to p53 suppressions that Bax, p53, and cytochrome C and reduce the activity of Bcl2 gene and leading to apoptosis. In case of Glycyrrhizic acid the P53 can lead to apoptosis majorly through p53 suppressing genes such as PUMA, NOXA and Bax. Schisantherin-A a hepatoprotective agent acted via P53 mediated pathway negatively regulates pregnane-X receptor activity, indicating that wuzhi activates PregnaneX receptor via inhibition of the p53 pathway. For Resveratrol also known as Zhi-shi blocked apoptosis by p53 down-regulated apoptosis regulator PUMA, AMPK-SIRT and JNK pathways. Curcumin acted via mechanism of apoptosis that can be reduced via p53 suppression through the initiation of caspase cascade regulation. Where, independent type mechanism occurs when p53 induces the transcription of a gene encoding protein such as the Fas which is essential to promote apoptosis. On the other side, the dependent type mechanism involves when p53 initiates Bax factors. Catecin acted via mechanism as P53, Bax and Bcl-2 are major genes which controls the apoptosis. Mechanisms by involving the Bcl2, Bax and activation of caspases which induces apoptosis and catechin caused the down regulation of those p53 mediated proteins. Silymarin has shown the p53 suppressing activity by down regulating the production of apoptotic proteins, p53 mediated apaf 1, and reduced caspase 9 activities which leads to apoptosis and hence acts as neuroprotective for cerebral ischemia. Chlorogenic acid has shown suppressing activity on apoptosis and autophagy by suppressing expression of p53 and caspase-3 and leading to the neuroprotective action. Andrographolide has reduce vascular smooth muscle cells apoptosis via p38 related p53 suppression and Bax. Hence acts as neuroprotective action. And at the last, Rutin inhibits apoptosis via decreasing Bcl2 and increasing P53 suppressor gene, regulates the cell cycle. These all mechanisms of various natural p53 suppressor agents hence proved that these compounds acting as advancements are showing the suppressing activity and helping in the cytoprotective activity.

6 CONFLICT OF INTEREST

Authors declare no conflict of interest.

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