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A Review on Inhibition of RAGE via Marine Sources, Herbal Sources and Food Substances

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Abstract: *Receptor for Advanced Glycation End-products (RAGE), also known as AGER,is a 35 kilodalton transmembrane receptor of the Immunoglobulin super family. Its name is mainly due to its ability to bind to advanced glycation end products (AGE), including glycoproteins and glycans which have been modified non-enzymatically through the Maillard reaction. RAGE is referred to as a Pattern Recognition Receptor. Studies have determined the contribution of protein glycation to disease-states and have mainly aimed at the harmful effects and mechanisms of these glycotoxins. Thus, the development and testing of AGE inhibitors, especially natural anti-AGE formulations, i.e. RAGE inhibitors without any side effects, may provide a therapeutic approach. In particular, the pursuit of RAGE inhibitors using in vitro and in vivo models identifies naturally occurring compounds for preventing glycation. This leads to inhibition of RAGE. Synthetic compounds also can inhibit the RAGE. Available data suggests that natural and synthetic compounds which have certain chemical constituents, may attenuate glycation, and can lead to RAGE inhibition via Natural as well as synthetic Sources.*

Keywords: RAGE, Maillard reaction, Vascular Endothelial Growth Factor (VEGF) and Resveratrol.

I. INTRODUCTION

1.1 Age Formation and their Involvement in Diseases

Advanced glycation end product (AGE) is a heterogeneousgroup of compounds formed by Maillard reaction, whichrefers to a non-enzymatic glycation of free amino groups of proteins,lipids or nucleic acids by reducing sugars and reactive aldehydes. In ourbiological system, the formation of AGE occurs after hyperglycemia or oxidative stress. AGE is also produced by reversing the Schiff base, a reversible formation attached to the covalently bound products of the Amadori rearrangement(Wu *et al.*, 2011). Amadori products follow certain chemical reactions that trigger the production of AGE. Formation of AGE is a part of body's normal metabolism.But, if it is too high, it can enter the tissues and bloodstream, causing pathological conditions(Ramkissoon *et al.*, 2012). Their toxic effect is mainly associated with the ability to stimulate oxidative stress and inflammation by binding to cell surface receptors or cross-linking with body proteins, altering their structure and function. Different studies on mice and humans have demonstrated that AGEs can be absorbed at intestinal level, and be potentially toxic.

1.2: Rage and its Physiology

AGEs have a receptor, which is termed as RAGE (Receptor for Advanced Glycation End Products), also known as AGER.Its name is derived from its ability to bind to advanced glycation end products (AGE), which includes mainly glycoproteins and glycans which have been modified non-enzymatically through the Maillard reaction. RAGE is a Pattern Recognition Receptor(Ramasamy *et al.*, 2008). It plays a very important role in the bodyacting as a cell surface receptor. RAGE is a multiligand receptor for the immunoglobulin cell-surface family of molecules that acts as a receptor for various molecules. The involvement of RAGE in pathological or physiological processes has been

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demonstrated in rat chronic disease models using sRAGE (soluble RAGE), counteracting RAGE antibodies, or forms of dominant negative receptors. Studies on RAGE mice confirms that RAGE partially contributes to the development of progressive complications of diabetes, such as neuropathy and nephropathy, macrovascular diseases and chronic inflammation(Sadowska-Bartosz and Bartosz, 2015). Deletion of RAGE provides protection from the lethal effects of septic shock caused by cecal ligation and puncture (CLP). Elimination of RAGE does not affect delayed host hypersensitivity. Despite the lack of effect observed inadaptive immunity by the deletion of RAGE, administration of the receptor decoy, sRAGE, still has a protective effect in RAGE mice. Thus, sRAGE is a type or behave like sequester ligands, that's prevent their interaction another receptorin addition ot RAGE. These data show that, RAGE is a multiligand receptor, its ligands can recognize multiple receptors when it mediates biological effects. RAGE can bind to several ligands and activate various signal transduction pathways that cause varioussubsequent effects(Burstein *et al.*, 2018).

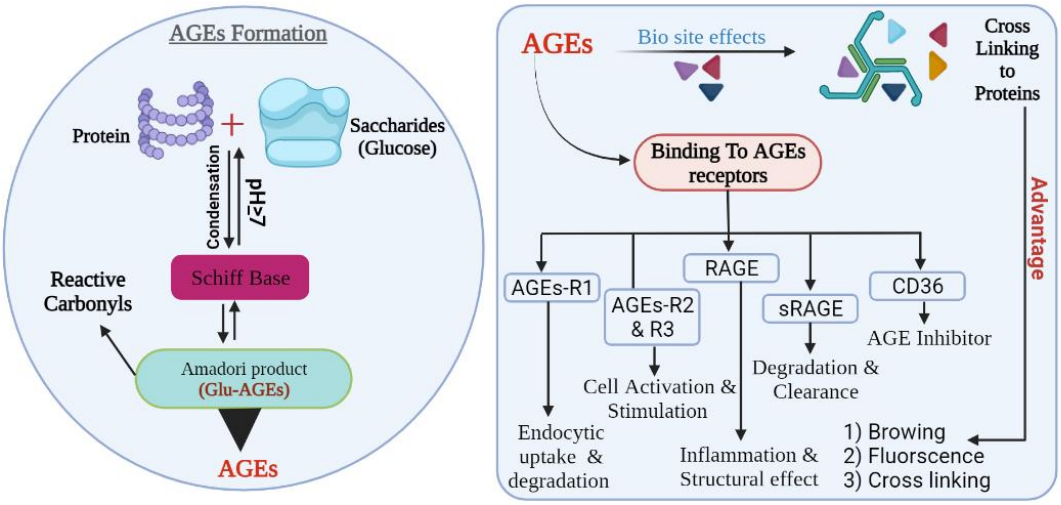

Figure: Schematic representation of AGEs formation and of their biological effects this illustration are created by the helps of BioRender software with free excess.

II. TYPES OFRAGE INHIBITORS

RAGE inhibitors of glycation, mainly using *in vitro* models, has identified natural compounds able to prevent glycation. There are many types of natural anti-glycating agents may attenuate glycation. This can lead to RAGE inhibition via Natural as well as Synthetic Sources.

Natural Rage inhibitors are derived from Marine,Herbal and Food Source areasfollow: -

1. Marine Source - Silymarin and Scalarin
2. Herbal Source - Rosemary, Hyperoside and Yerba Mate
3. Food source – Resveratrol, Vitamin A (Retinol), Quercetin, Tomato paste

fraction, Chestnut(*Castanea sativa)*and Edible Mushroom (*Lactarius deterrimus)*

Synthetic RAGE inhibitors are as follows

1. Heparin,
2. Azeliragon (or PF-04494700),
3. Sodium sulphite,
4. N-acetylcysteine,
5. Pyrazole-5-carboxamide,
6. 4,6-bisphenyl-2-(3-alkoxyanilino)pyrimidine,
7. 3-(N,N-dimethylamino)pyrrolidine,
8. Aminoguadine,

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9. Papavarine,
10. Iridoids.
11. FPS-ZM1
12. Pioglitazone
13. P4 789
14. PF 04494700

III. RAGE INHIBITORS FROM MARINE SOURCES

3.1 SILYMARIN

The marine compound Silymarin which is extracted from the dry seeds of milk thistle [*Silybum marianum* (Asteraceae)] has potent antioxidant properties. It containsmixture of seven flavonolignans; silybin A, isosilychristin, silybin B, isosilybin B, isosilybin A, silydianin, and silychristi, and the flavonoid taxifolin. It has been used for decades in the treatment of liver diseases such as liver cirrhosis and chronic hepatitis.

To determine the ability of Silymarin which counteracts AGE-induced effects by a GSK-3β-mediated Vascular Endothelial Growth Factor (VEGF) cells, the Human brain microvascular endothelial cell line, HBEC-5i were used(Alhusban, Alkhazaleh and El-Elimat, 2017).The most probably HBEC-5i cells were treated with silymarin in two different doses (50 and 100 μM). Angiogenic assays like Cell migration assay and Tube formation assays were performed.

Cell Migration Assay: The migratory capacity of HBEC-5i was measured using this assay. Cells were cultured in a 12-well plate to about 80% convergence prior to the serum kept for 24 hours. A scratch was initiated in the cell monolayer using a 1 mL micropipette tip, and the media was again displaced by fresh serum-free DMEM:F12 media. The different treatments were given, as and accordingly. Front images of the scratch edges were captured or takenby using a digital camera mounted on an inverted microscope at baseline and 16 hours after treatment procedure. The migration rate (migrant efficacy) was determined by measuring the distance between the scratch edges at both time points. The migration rate was calculated by subtracting the scratch width at 16 hours from the width measured at baseline and dividing it the width at baseline. The wound recovery rate was presented as a percentage of the recovery rate of the control.

Tube Formation Assay (*in vitro*):The fixed number of cells were added as per based on assay procedure, 20,000 total number of cells per well were added to a Cultrex® basement membrane extract-coated 96-well plate. All plates was coated with the Cultrex base (base layer/basement) membrane extract. The rate of tube formation was measured by counting the number of tube-like structure between 6 and 8 hours after treatment application in three non-overlapping images of each well.The HBEC-5i angiogenic potentialwas evaluated by cell migration and *in vitro* tube formation capacities.AGE significantly increased the cell migration and tube formation rates of HBEC-5i. Silymarin ameliorates the AGE-induced migration in a dose-dependent manner; where 50 μM reduced migration by about 50%, whereas the 100 μM completely inhibited AGE-induced migration.This concludes that, Silymarin inhibits the RAGE receptor and results in the inhibition of AGE-induced abnormal angiogenesis in a GSK-3β-mediated inhibition ofVEGF(Guzmán *et al.*, 2019).

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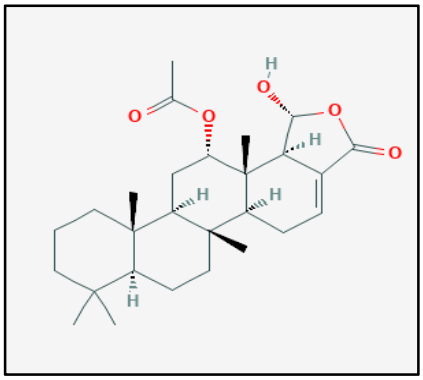
3.2 SCALARIN



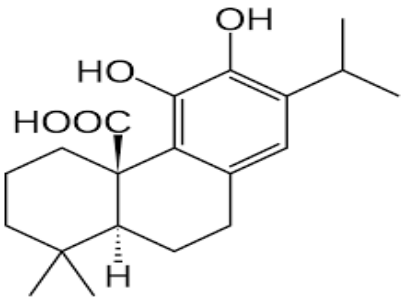
Scalarin is a sesquiterpene natural product isolated from a marine sponge, *Euryspongia rosea*.The Receptor for Advanced Glycation Endproducts (RAGE) has emerged as a chemotherapeutic target in KRAS(or Ki-ras) determined pancreatic cancers for the treatment as well as in chemoprevention. RAGE are an important regulator of inflammatory, stress and survival pathways that lead to carcinogenesis, resistance to chemotherapy, enhanced proliferation and the high metastatic potential of pancreatic cancer. RAGE expression has been demonstrated in pancreatic cancer tumors (but not in adjacent epithelial tissues). The presence of RAGEthat are associated with metastasis and increasing. In an effort to identify novel inhibitors of RAGE, a marine-derived secondary metabolite; cell-based screening assay utilizing flow cytometry was developed (Guzmán *et al.*, 2019).The scalarin stock solution was dissolved inmethanol 1 mg/mL.For cell viability assaysthe 3-[4,5-Dimethyl-2-thiazolyl]-2,5-diphenyl-2H-tetrazolium bromide (MTT) was used.The human pancreatic cancer cell lines PANC-1(CRL-1469), AsPC-1 (CRL-1682), BxPC-3 (CRL-1687) andMIA PaCa-2 (CRL-1420) cell lines were grown and maintained in liquid nitrogen.

For RAGE Inhibition screening assay, PANC-1 cells were placed in aU-bottom plate and allowed to keep overnight. Cells were harvested by adding cell dissociation buffer (0.05%collagenase I in trypsin solution) containing 7-aminoactinomycin D (7AAD) to each well. 7AAD is cell impermeableandenters cells that are dead or at the final stepsof cell death. Cells were made into pellets by centrifugation, fixed with4% p-formaldehyde in Phosphate Buffer Saline and permeabilized with ice coldmethanol. It reduces RAGE expression 30 to 50% in these cell lines.Scalarin shows little cytotoxicity in the screening assay and its IC50 for cytotoxicity ranges between 20 and 30 µM in the AsPC-1, PANC-1, MIA PaCa-2 and BxPC-3 pancreatic cancer cell lines. A desirable property of scalarin is used to suppress secondary tumor formation in the chemotherapies. Thus, Inhibition of RAGE in pancreatic cancer cells was carried out by scalarin suggesting that it may merit further studies in the future.

IV. RAGE INHIBITORS FROM HERBAL SOURCE

4.1 ROSEMARY

Rosemary Plant



Carnosic Acid (CA)

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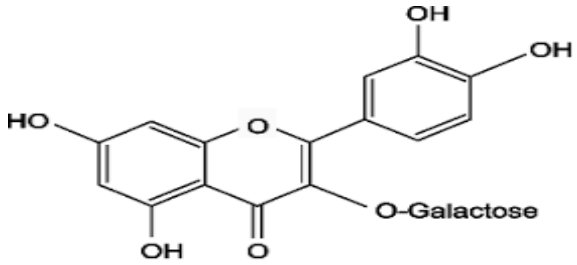
Rosemary is a woody, perennial herb with fragrant, evergreen, needle-like leaves and white, pink or purple flowers, biological name *Rosmarinus officinalis* and family Lamiaceae.It is well-known for its antioxidant properties and has been widely used as a preserving agent in the food industry, cosmetic additives, and nutritional supplements.Rosemary contains a variety of polyphenolic compounds, including carnosic acid (CA), carnosol, rosemanol, rosmarinic acid (RA), and many others.Among these compounds, Carnosic acid is used as a principlecomponent for the standardization of commercial rosemary extract. The preventive effects of carnosic acid, as a major bioactive component in rosemary extract (RE) were evaluated on high-fat-diet-induced obesity and metabolic syndrome in male mice(Zhao *et al.*, 2015). The mice were given a low-fat diet, a high-fat diet supplemented with CA-enriched RE (containing 80% CA) or RE (containing 45% CA), for a period of 16 weeks. The dietary RE supplementation significantly reduced body weight gain, percent of fat, glucose, insulin levels, liver weight, liver triglyceride, and free fatty acid levels in comparison with the mice fed with a High Fat diet without RE treatment. Increase in the liver GSH/GSSG ratio was observed to determineantioxidant activity compared with High Fat group. The RE suppresses RAGE and it brings about its down-regulation. The results demonstrate that Rosemary inhibits RAGE and it is a prominent dietary agent to reduce the risk of obesity and metabolic syndrome.

4.2 Hyperoside



Hyperoside is a flavonoid compound of herbal plants which are traditionally used in Chinese medicines for their neuroprotective, anti-inflammatory, anti-oxidative and vascular protective effects. Hyperoside is a major active constituent in many medicinal plants like St.John's wort.

It was hypothesized that hyperoside may inhibit JNK activation and promote ECV304 cell proliferation. TheRAGE could mediate the intracellular signals in ECV304 cells initiated by AGEs, resulting in activation of the c-Jun *N*-terminal kinases (JNK) pathway and apoptosis in ECV304 cells by its inhibition(Zhengyu Zhan 2014). An experimentalsystem to study of the effects of RAGE on JNK activation in response to AGEs was demonstrated by transfecting dormant ECV304 cells with siRNA-RAGE.Human cell line ECV304 (derived from urinary bladder carcinoma) were cultured and supplemented with 10% fetal calf serum, penicillin and streptomycin.ECV304 cell transfection was performed. The small interfering RNA (siRNA-RAGE) of RAGE were synthesized. Serum-starved ECV304 cells were subjected to AGEs and hyperoside for 10 minutes for Western blot analysis, and cultured for 48 hours for MTT assays. EVC304 cells were germinated in 96-well culture plates at 3000 cells per well. After incubation at 37 °C for 24 hours, the medium was replaced with fresh medium supplemented with hyperoside (50 µg/mL). After an hour, AGEs (200 µg/mL) were added to the cells for 10 min. Stock Solution was added to each well and the absorbance was measured at 570 nm using an ELISA. Cell viability was calculated relative to untreated cells.The membranes were probed with antibodies against phosphorylated JNK and reprobed with β-actin antibody. Chemiluminescence (ECL) detection system was used for the visualization of bands. Densitometry were used for the quantified the intensities of bands.

This studyproves the potential of hyperoside in mediating the intracellular signaling pathways initiated by AGEs, by inhibiting the effects of RAGE, thereby suppressing JNK activation and increasing cell proliferation in ECV304 cells. It suggests the role of hyperoside through blockade of the RAGE signaling as a therapeutic method for preventing cardiovascular diseases. This research may advance understanding of the effects of AGE on vascular remodeling and contribute to the study of vascular diseases and diabetes.

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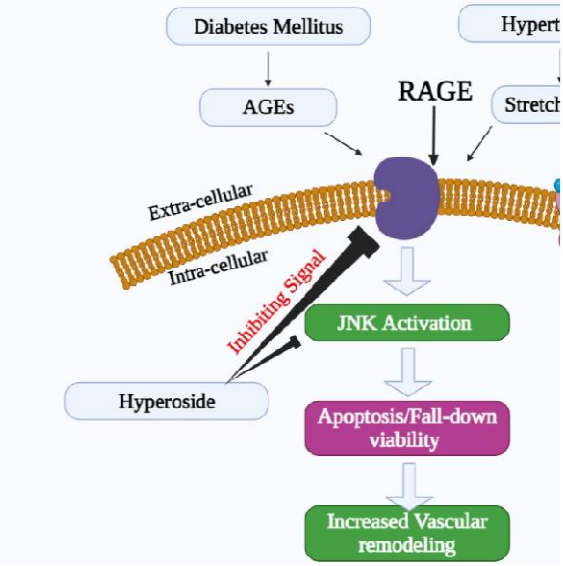

Diagram (all over illustration created by using BioRender software) that showing the potential role of the RAGE signaling pathway in the presence of AGEs action on the JNK activation and ECV304 viability inhibition. Increased blood sugar (diabetes) can trigger an increase in AGEs on the walls of vein grafts and arteries. There are some other factors may cause such as; AGEs can be cause ECV304 cells deformation, activation of RAGE by AGEs and its signaling molecules of downstream process, including JNK. Activated JNK (P-JNK) leads to over expression of RAGE and viability inhibition of ECV304 cells (MTT), altering vascular structure and function. Blocking RAGE and its downstream molecules by Hyperoside can inhibit vascular remodeling induced by AGEs.

4.3 Yerba Mate

Yerba mate, *Ilex paraguariensis*, family Aquifoliaceae, is found mainly in energy drinks, as well as in a bottled or cannediced tea. It contains Xanthenes- caffeine, theobromine and theophylline. The major component is caffeine. It may also contains trace elements such as potassium, magnesium and manganese.

The polyphenol-rich *Ilex paraguariensis* (IP) extract was capable of inhibiting advanced glycation end-products(AGEs) formation as well as for the inhibition of RAGE. TheextractIP effects on AGE fluorescence generated on the BSA (bovine serum albumin) by glycation with methylglyoxal were demonstrated(Lunceford and Gugliucci, 2005). The effect of IP extract may be due to the different composition in phenolics of the botanical preparations. To discriminate between an antioxidant and a carbonyl, tryptophan fluorescence and cross-linking by sodium dodecyl sulfate polyacrylamide gel(SDS-PAGE) electrophoresis was performed. The changes induced by glycation and substitution of

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positive charges in arginine and lysine produce a decrease in tryptophan fluorescence. It is shown that incubation of BSA with methylglyoxal produces subsequent changes in tryptophan fluorescence. All over this types of reaction or pathway prevents the downstream effect or properties of AGE formation. Some results from the process of SDS-PAGE are; therefore by the inhibition of the second phase of the glycation reactions that cause, conversion of the Amadori products to AGE by the help of free-radical mediated. Results demonstrate a significant, dose-dependent effect of IP extract on AGE adducts formation on a protein model *in vitro*. The inhibition of AGE formation was obtained and we can conclude that, *Ilex paraguarensis* inhibits RAGE as well.

4.4 Arbutin

Arbutin (hydroquinone-D-glucopyranoside) is a naturally occuring compoundfound in various plant species of diverse family such as Ericaceae (*Arctostphylos*), Betulaceae, (*Betula alba*) and Rosaceae (*Pyrus communis*.). It is used as a skin-whitening agent in cosmetics due to its inhibitory effect on tyrosinase activity. Arbutin possesses antioxidative and free radical scavenging properties. It was determined that Arbutin shows an antiglycation activity when tested *in vitro* by the glucose-BSA assay.

Glycation inhibitory activity of arbutin was performed by using an *in vitro* glucose-bovine serum albumin (BSA) assay(Jedsadayanmata, 2005). Glucose and BSA were incubated at 60ºC in presence of arbutin. Following a 24-hour incubation period, the glycated BSA product was precipitated with trichloroacetic acid (TCA) and dissolved in alkaline phosphate buffered saline (PBS). Basically, the glycated BSA formationwas relatively quantitated by measuring of fluorescence intensity. Antiglycation assay was performed accordingly. The final reaction volume was performed in 1.5-ml Eppendorf tube. Albumin (1 mg/ml finalized concentration) were incubated with the glucose of (500 mM final concentration) in the occurrence of arbutin. The reaction was stopped by adding 10 µL of TCA. The TCA-added mixture was kept at 4ºC for 10 minutes before centrifugation. Results demonstrated the antiglycation activity of arbutin and its ability to inhibit the formation of glycated BSA by glucose in a dose-dependent manner. The minimum 50% inhibition was observed at 5 mM concentration of arbutin. Its inhibitory activity was further confirmed when the glycation reaction that was allowed to proceed at lower temperature (37ºC) for same findings in regular 14 days. These all results and data indicated that arbutin shows an *in vitro* antiglycation activity. In presence of arbutin, the intensity of fluorescent was significantly decreased at every time, that's indicated the less formation of glycated BSA. Thus, we can conclude that, arbutin, a naturally occurring compound with antioxidative and radical scavenging activity, possesses an *in vitro* antiglycation activity based on glucose-BSA assay and hence, it can lead to the inhibition of RAGE.

V. RAGE INHIBITORS FROM FOOD SOURCES

5.1 Resveratrol

Resveratrol (3,5,4′-trihydroxy-*trans*-stilbene) is a stilbenoid, a type of natural phenol, and a phytoalexin produced by several plants in response to injury or, when the plant is under attack by pathogens, such as bacteria or fungi.Ithas various bioactivities, including estrogenic, anti-platelet, anti-inflammatory and antioxidanteffects.Sources of resveratrol in food include the skin of grapes, blueberries, raspberries, mulberries, and peanuts. It is a natural polyphenolic antioxidant.

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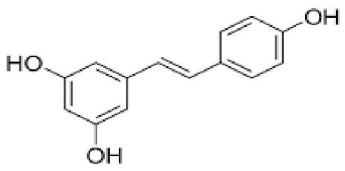
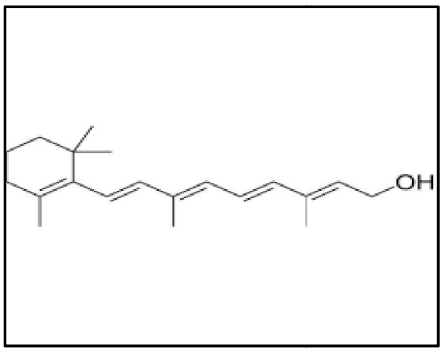


Structure of Resveratrol

Studies claim that , Resveratrol prevents the impairment of advanced glycosylationend products (AGE) on macrophage lipid homeostasis by suppressing the RAGE via peroxisome proliferator-activated receptor activation(PPARɣ)(Buttari *et al.*, 2013).Resveratrol selectively activates peroxisome proliferators-activated receptors (PPAR).Phorbol myristate acetate (PMA), resveratrol, PPARɣ inhibitor GW9662 along with antibodies against human CD36,SR-A, ABCA1 and ABCG1 were used for immunoblotting. Counteracting antibody against human RAGE was used to block bioactivity of AGE and also used for immunoblotting.Immunoblot analysis was performed .Cells were lysed in high-salt extraction buffer and a protease inhibitor, placed at -20˚C for 20 min, and centrifuged at 4˚C for 20 minutes to remove insoluble material. Lysates (20µg) were separated by SDS-PAGE, transferred to polyvinylidene difluoride membranes, and probed with the antibody against indicated protein. After incubation with secondary antibodies for 2 hours, proteins were detected by enhanced chemilum inescence. ß-actin was used as a loading control. Proteins of interest were expressed as the ratioagainst ß-actin. Resveratrol pre-treatment led to a dose-dependent suppression of AGE-induced RAGE expression. 75% expression of RAGE suppressed by the Resveratrol (10 µmol/l). The expression of PPARɣ and phosphorylated AMPK (p-AMPK) were the potential targets of resveratrol. The effect of resveratrol on RAGE expression were inhibited by the presence ofGW9662, a selective antagonist of PPARɣ. It suggests that the suppression of resveratrol on macrophage RAGE expression was PPAR ɣ-dependent.

In conclusion, the results strongly indicate that resveratrol prevents the AGE-induced acceleration of macrophage lipid accumulation through suppression of RAGE via PPARɣ activation, which suggests new strategies to prevent diabetic atherosclerosis.

5.2 Vitamin A(Retinol)



Structure of Retinol

Vitamin A are a group of unsaturated nutritional organic compounds. It includes retinol, retinal, retinoic acid, and β-carotene. Vitamin A has multiple functions. It is important for growth and development, for the maintenance of the immune system, and for good vision. The major form of vitamin A is an ester, retinyl palmitate, which is converted to retinol in small intestine. Studies demonstrated that Vitamin A (retinol) inhibits the receptor for advanced glycation

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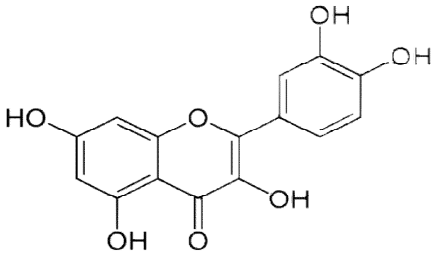
endproducts (RAGE) by oxidant-dependent activation of p38 MAPK and NF-kB in human lung cancer A549 cells(Gelain *et al.*, 2011)

Experimental works in cell cultures and animal models showed that retinol may induce free radical production, oxidative stress and extensive biomolecular damage. The effect of retinol is evaluated for the regulation of the Receptor for Advanced Glycation End-Products (RAGE) in the human lung cancer cell line A549.The cell lines were treated with retinol therapeutic doses (10 or 20 μM). Retinol at 10 and 20 μM increased free radical production, oxidative damage, and antioxidant enzyme activity in the cell lines. p38 MAPK activation is the mediated between the effect of retinol on RAGE. Retinol induced a redox-dependent activation of MAPK. It was observed that NF-kB acted as a downstream effector of p38 in RAGE inhibition by retinol. The results show a pro-oxidant effect of retinol on cell lines, and suggest that inhibition of RAGE expression by retinol is carried out by the redox-dependent activation of p38 or NF-kB signaling pathway. This also indicates that RAGE inhibition by retinol is mediated by the free radical-dependent activation of p38 and Akt.

5.3 QUERCETIN



Quercetin is a plant flavonol from the flavonoid group of polyphenols. Mostly it found in many of vegetable, fruits, leaves, and grains. It is abundant in apples, grapes, red raspberry, and onions. It has a bitter flavour and is used as an ingredient in dietary supplements, beverages, and foods. Quercetin has been reported to inhibit the oxidation of other molecules and hence, it is an antioxidant. It contains a polyphenolic chemical sub-structure that stops oxidation by acting as a scavenger of free radicals that are responsible for oxidative chain reactions.

The triggering of gemcitabine(GEM) drug resistance with Quercetin in pancreatic cancer by RAGE inhibition was demonstrated. The research evaluated the mechanisms of quercetin in regulating cell death and enhancing drug effects through RAGE inhibition, especially in GEM-resistant pancreatic cancer cells(Lan *et al.*, 2019).

Human pancreatic cancer cell lines MIA Paca-2, bxpc-3, aspc-1, HPAC and PANC-1 wereused. A stable GEM-resistant pancreas carcinoma cell line (designated MIA Paca-2 GEMR cells) was established from 0.05 mm GEM concentration for developing a cellular model tolerance. All tumor cells were maintained and cultured in an incubator supplemented with 5% CO_2 at 37ºC. The stimulants, GEM and Quercetin were used.MTT assay was performed. Quercetin has proven to be an outstanding anti-cancer potentialdue to its anti-proliferation effect and roles in cell cycle arrest, the induction of apoptosis, and the inhibition of cellinvasion. Significantly RAGE expression inhibited in MIA Paca-2 cells due the treatment with quercetin. It was observed that the RAGE knockdowns the cells, autophagy, apoptosis under quercetin treatment in MIA Paca-2 cells.Autophagy, apoptosis, and chemosensitivity were greatly increased by the additional effect of quercetin combined GEM treatment in MIA Paca-2. These results indicate that inhibiting RAGE significantly increases cell death and GEM-induced cytotoxicity through the PI3K/AKT/motor axis in MIA Paca-2 and MIAPaca-2 GEMR cells. Quercetin treatment effectively attenuated RAGE expression, suggesting that an additional reaction occurred under combined quercetin and GEM treatment. This study provides direct evidence forrevealing the molecular mechanisms of quercetin in increasing autophagy, apoptosis, and chemosensitivity in pancreatic cancer.Quercetin showed a dramatic effect on RAGE inhibition occurring under combined quercetin-gemcitabine treatment. It concludes that, the results demonstrated that the molecular mechanisms of quercetin in regulating apoptosis and autophagy-related pathways and increasing GEM chemosensitivity in pancreatic cancer cells involved inhibition of RAGE expression.

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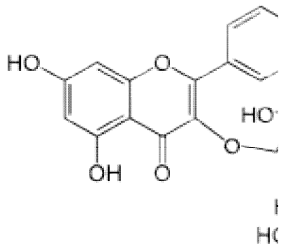
5.4 Tomato Paste Fraction

Tomato Paste



Rutin

The tomato has more number of anti-inflectional properties which is important for human beings, the edible red, berry of the plant *Solanum lycopersicum*, commonly known as a tomato plant. Tomato paste is a thick paste made by cooking tomatoes for several hours to reduce the water content, straining out the seeds and skins, and cooking the liquid again to reduce the base to a thick, rich concentrate.

A water-soluble and low-molecular-weight fraction (SB) was obtained and the effects of SB on the formation of AGEs in protein glycation were studied by the methods of specific fluorescence, ELISA and a Western blot analysis, using the anti-AGE antibody after incubating protein with sugar(Kiho *et al.*, 2014).

The results suggest that SB had strong inhibitory activity and that the inhibitory mechanism of SB involved trapping of reactive dicarbonyl intermediates in the early stage of glycation. SB, due to containing an antioxidant, Rutin, that's showed potent inhibitory activity. Rutin chiefly contributed to inhibiting RAGE, and other compounds in SB may also have been related to this activity.

Bovine serum albumin (BSA) (fraction V, fatty acid-free), N-acetyl-glycyl-lysine methyl ester(GK-peptide), and o-phenylenediamine dihydrochloride tablet sets were used for the experimental study. The horseradish peroxidase-conjugated anti-AGE mousemonoclonal antibody and rutin were used.

Fractionation of Tomato Paste by using - Tomato paste (10 kg) was centrifuged for five minutes at 6000 rpm to give a supernatant (9.05 kg) and precipitate (0.95 kg). The supernatant was ultra-filtered through a membrane under a pressure of 0.1 MPa to separate the non-filtered fraction (SA, 1.81 kg) and filtered solution (SB, 7.2 kg). Partition between SB (5 ml) and an equal volume of n-butanol was performed to give n-butanol fraction (SB-BU). Part of the SB solution(2 ml) was applied to a small column of active carbon and eluted with water, the fraction being collected to give SBC (the total volume was adjusted with water to2 ml). Half this amount of SBC(1 ml) was reduced withNaBH4, the total volume of SBCR was adjusted with water to 1 ml. Therefore, SB which contained 23 mg of sugars (glucose)per ml was obtained by fractionating tomato paste.

Fluorescence as a parameter was used to study the influence of SB on the formation of AGE in the BSA or a glucose system, because specific fluorescence increases during the process of glycation and SB results a decrease in fluorescence. Inhibition percentage rate was calculated from the result of Western blot technique with the horseradish peroxidas e-conjugate dantigen-AGE antibody

The percentage inhibition was calculated from the results of the Western blot analysis with the horseradish peroxidase-conjugated anti-AGE antibody. Aliquots of the incubation solution in the BSA or a glucose system were analyzed by the ELISA technique with the horseradishperoxidase-conjugated anti-AGE antibody. Glycation Inhibition by Tomato Paste fluorescence intensities was observed during the incubation. Therefore, SB showed an inhibitory effect on the formation of AGE in the experiment with fluorescence as a parameter inthe BSA or a glucose system. Since AGE is known to be fluorescent and non-fluorescent compound and SB itself slightly affects the fluorescence, the inhibitory effect of SB on AGEformation in the BSA or a glucose system was analyzed by Western blotting with the anti-AGE antibody. SBshowed a dose-dependent inhibitory effect, the percentage inhibition of 50 % and 100% of SB being morepotent. A component, Rutin in SB was determined by HPLC to contain a water-soluble antioxidant and an aldose

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reductase inhibitor. More probably Rutin in SB show chiefly contribution to the inhibition. The results suggest that Rutin was related to the inhibition, although other inhibitory compounds in SB have not yet been determined. SB was also shown by ELISA to have a potent inhibitory effect on the formation ofAGE in the BSA or a glucose system.

This concludes that, the water-soluble and low-molecular-weight fraction (SB) prepared from tomato paste strongly inhibited the formation of AGEs in the glycation process by the analyses of fluorescence, Western blotting, and ELISA *in vitro* tests.

5.5 Mushroom (*Lactarius Deterrimus)* and Chestnut(*Castanea Sativa)*

Lactarius deterrimus

Castanea sativa

Edible mushroom, *Lactarius deterrimus*, this species of fungi kingdom also pronounces by different terms such as orange milkcap or false saffron milk cap, from the family Russulaceae, has various biological activities. It is used for different types of prevention and treatment of various diseases or disorders. *Lactarius deterrimus* and their chemical active compounds have been described to possess antioxidant properties and therefore, it most gives to diabetic patients and play important role in the management of diabetes.

Sweet chestnut, *Castanea sativa* from the Fagaceae family, is a known source of phenolic (aromatic compounds of benzene ring) bioactive compounds. It has been widely used in folk medicine for treating various types diseases. In recent studies that's shown that the *Castanea sativa* extract possesses antioxidant properties also has extensive ability to prevent DNA damage from various types of factors.

Overall output of this present study aimed to investigate some beneficial effects of the treatment with extracts from the chestnut *Castanea sativa* (Cs) and edible mushroom *Lactarius deterrimus* (Ld), by separately and in combination (Mixture Ld/Cs), on oxidative stress and advanced glycation end-product (AGE)-mediated hepatorenal injury in a rat model of streptozotocin (STZ)-induced diabetes (*in vivo*) by examining pathways responsible for maintenance of redox homeostasis.

These experimental models of both diabetes was induced in rats by the administration of 40 mg/kg STZ intra-peritoneally (i.p.) for 5 consecutive days. Experiments were performed on 2.5-month-old adult albino Wistar rats weighing 220–250 grams. Finalized extract product were applied separately (with their maintaining concentration) at a dose of 60 mg/kg i.p. and in combination (60 mg/kg each extract; i.p.) for one month or four weeks, starting from the last day of STZ administration (from ADME). A single mode of administration was chosen to be i.p. because rats refused to drink the extract due to its bitterness STZ was dissolved immediately before use in sodium citrate buffer (0.1 M, pH 4.5). Also, one factor most important for the measurement of blood glucose after 24 hours of last STZ injection. After taking blood sample (overnight fasted rat) from the tail vein of rat and measured inside the blood glucometer. All rats was considered to have diabetes when the measuring the fasting blood glucose level exceeded 20 mmol/l. After the four weeks of time due to diabetes. Some steps are followed such as; collection of blood sample, abdominal incision was made, both of kidney & liver removed and processed further as indicated or showing with timeline. All collected samples (kidney and liver tissue sample) were cryopreserved inside the -80°C temperature and used after that for nuclear protein and cytoplasmic preparation. Hepatorenal function improvement is most important in diabetic rats

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which are treated with the extracts, that was associated with an improved lipid status and glycemic & also oxidative stress suppression (oxidative damage of DNA and lipids).

These two extracts probably inhibited protein glycation and *in vitro*AGE formation, they may help in the reduction of non-enzymatic glycosylation in diabetic rats *in vivo*. Here we were observed the antiglycation activity of the examined extracts (separately and in combination) was accompanied with the inhibition of CML-mediated RAGE/NF-κB activation and reduction of enzymatic *O*-GlcNA cylation in liver and kidney tissues of diabetic rats. These results reveal that the administration of chestnut and mushroom extracts, either individual or in combination, activates a coordinated cytoprotective response against diabetes-induced hepatorenal injury not only through the antioxidant defense system cell recovery, also marked antiglycation activities.

Some types of potential inhibitory effects of the separate extracts were examined during the process of protein glycation. The concentration ranges is directly related to the ability of the examined extracts to suppress glycation, was dose-dependent in the case of both extracts, while the combination of the two extracts exhibited the strongest anti-glycation activity. During extracts addition to reaction media that's contained the fructose/BSA/glucose system, inside the fluorescence the significant eject concentration-dependent reduction efficacy intensity was observed during the last time line of this study.

Results show that treatment with extract interrupts the cycle of CML-mediated RAGE or the NF-κB activation by decreasing protein glycation and CML formation in both tissues, indicating that both examined extracts gives a strong anti-glycating activity *in vivo*. Decrease in CML levels, as observed in *Castanea sativa* extract-treated diabetic rats could give the output as improved hyperglycemia.

On the other hand, the prominent anti-glycating activity of the *Lacterius deterrimus* extract observed in liver and kidney tissues of diabetic rats, despite of its weaker antihyperglycemic activity could be the result of antioxidant effect. Two concentration ranges differed for extracts. The inhibition of NTB reduction, that's directly related to the ability of the examined of the extracts to suppress glycation, which is dose-dependent in the case of both extracts, while the combination of the two extracts exhibited the strongest anti-glycation activity, providing nearly 80% inhibition of NTB reduction. The combination of these extracts showed the greatest effect inhibiting the RAGE by 90%.

Hence, we can conclude that types of administration of mushroom extracts and chestnut, either individually or in combination, improved the diabetic complication such as infectious or pathological conditions of liver and kidney cells functions. The beneficial effect of the examined extracts was achieved not only by reducing the glucose-triggered overproduction of free radicals, but also through a marked anti-glycation activity. The extracts significantly reduced non-enzymatic glycosylation in diabetic rats *in vivo*, which leads to inhibition of CML-mediated RAGE and NF-κB activation of enzymatic *O*-GlcNA cylation in liver and kidney tissues. This has a positive impact on various cellular processes, delaying the progression of the diabetic complications. This study may be relevant with regard to the therapeutic potential of chestnut and mushroom extracts in treating the diabetic condition and also in the management of oxidative stress in other pathological states.

5.6 Sweet Potato

The preventive effect of purple sweet potato (PSP) on high fat diet (HFD) induced obesity was determined along with its mechanism(Zhang *et al.*, 2015). Eight-week-old male Sprague Dawley rats were divided into 7 groups. They were administered PSP intra-peritoneally once in a day for 7 days. Obesity was prevented and abnormal glucose, triglyceride, and total cholesterol levels induced by the HFD for 6 weeks restored to nearnormal levels. PSP reduced the level of reactive oxygen species and inhibited the receptor of advanced glycation end products (RAGE). The anti-obesity effects of PSP were mediated via attenuation of oxidative stress and regulation of leptin or AMPK signalling in the hypothalamus. RAGE has been a molecular nutrient sensor associated with oxidative stress and energy metabolism. HFD administration increased the expression level of RAGE in the hypothalamus of rats, compared with controls. Only a high-dose of PSP suppressed the RAGE induced by the HFD-treatment, and there were no significant differences observed for low and middle-dose PSP group rats, compared with HFD-treated rats. Analysis of the mean optical density values of RAGE showed that the integral optical density values were the same. Immuno fluorescence results

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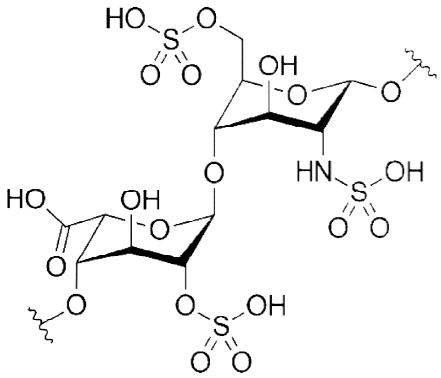
showed that RAGE directly binds with TXNIP, indicating that related regulatory triggering occurs among ROS, RAGE, and TXNIP. PSP effectively eliminated the obesity that was induced by administration of HFD and treatment efficacy results based on oxidative stress and inhibiting the RAGE signalling pathway. PSPimproved HFD induced obesity by blocking of endogenous oxidative, leading to repression of RAGE signalling and preservation of the leptin signalling capability. Activation of PI3K or AKT signalling in the hypothalamus resulted in phosphorylation of mTOR and further inhibition of AMPK activation, which regulated food intake and body weight.

VI. RAGE INHIBITORS FROM SYNTHETIC SOURCES

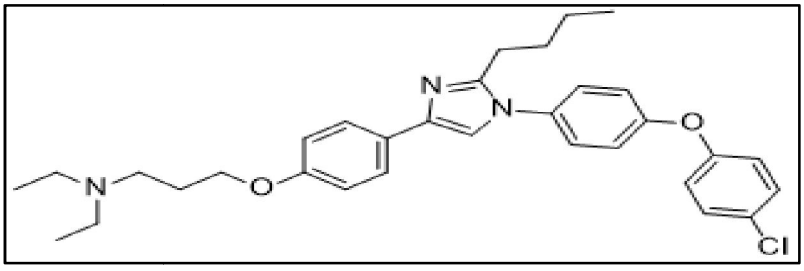
6.1 HEPARIN



Heparin, also known as unfractionated heparin (UFH), is a naturally occurring glycosaminogly can produced by basophils and mast cells in all mammals. As like different way of medication some anticoagulants (or blood clot remover). Specifically, it is also used in the treatment of heart attack and anginapectoris. It's given by intravenous or inside a vein by administer epidermis layer of skin.It's function as anticoagulant, that prevent the formation of clots and spreading of existblood clots within the blood or in blood vessels.

Self-association mode of RAGE occurred inside the living cells without any exogenous large molecule ligands. This self-association was partially inhibited by heparin. Heparin has a high content of sulphated L-iduronic acid units which binds to RAGE and inhibits the RAGE–ligand binding and dimerization. O- and N-sulphated K5 oligosaccharides were able to inhibit RAGE binding to amyloid β-peptide and HMGB1 at concentrations that are shown for heparin. For the strong inhibition the required size of oligosaccharides islie from 3100–5800 Da. Also, the heparin is not penetrated through cell membrane,all inhibition pathways are occurs on cell surface membrane. In the result the solubilized heparin may be interfere with surface layer of cell membrane of RAGE heparan sulphate interaction that's lead to dissociation of the RAGE homodimer. sRAGE dimerization is enhanced by heparin and dimerization at the cell surface is inhibited by heparenase treatment. The soluble heparin interferes with cell surface on RAGE. This shows that RAGE dimerization occurring in living cells can be inhibited by heparin. We can conclude that, RAGE ligand binding can be inhibited, also RAGE–AGE interactions and HMGB1 binding to heparin can be inhibited.

6.2 Azeliragon (or PF-04494700)



Structure of Azeliragon

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Azeliragon is an oral, small-molecule which is an inhibitor of RAGE. Azeliragon are bound to its receptors, then AGEs caused inflammation and oxidative damage. RAGE also binds Aβ, and has been reported to mediate toxic effects of Aβ oligomers in neurons. RAGE is upregulated in astrocytes and microglia in the hippocampus of people with Alzheimers disease and mediates amyloid transport into the brain. These types of interaction are blocks by RAGE antagonist Azeliragon.

Hence, the rationale is that it would provide a combined treatment effect across glial inflammatory and amyloid-related processes. In preclinical studies and analysis, different types of compound are used like, in transgenic miceAβ load decreased in brain and improved their relative performance on behavioral assays. Azeliragon (or PF-04494700), an oral inhibitor of receptor for advanced glycation end products, was regarded as safe in the diabetic patients with mild-to-moderate dementia of the Alzheimer type of diseases(Burstein *et al.*, 2018).

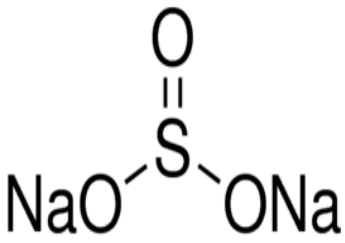
Patients aged 50 years and older who met the National Institute of Neurological and Communicative Diseases and Stroke or Alzheimer's Disease and Related Disorders Association criteria for Alzheimer disease with an Mini-Mental State Examination (MMSE) score between 12 and 26 (inclusive) were randomized to 10 weeks of double-blind treatment with either a 10 mg "low dose" and a 20 mg "high dose" of PF-04494700 with a Placebo. Some safety measures are included vital signs, adverse events, laboratory analysis, and 12 different leads of electrocardiogram.

A higher proportion of patients completed 10 weeks of double-blind treatment on both the "low-dose" regimen of PF-04494700 and the "high-dose" regimen than patients, who were on placebo. Discontinuation owing to adverse events and incidence of severe adverse events were lower in the "low-dose" regimen and the "high-dose" regimen compared with placebo. There were no clinical differences in vital signs, laboratory test results, or mean electrocardiogram parameters in patients treated with PF-04494700. We can conclude that Azeliragon or PF-04494700 inhibits the RAGE and weeks of treatment with PF-04494700 was safe and well tolerated in patients with mild-to-moderate Alzheimer disease.

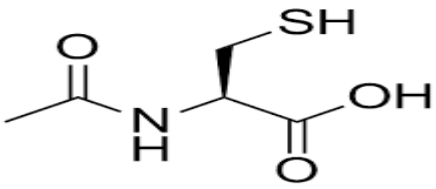
ROS act with AGEs and Aβ and form a complex at cellular membrane, stimulates the activation of cytokinesis and showing activation Astrocytes also treat the vascular disfunction (astrocytes act and form blood brain barrier also). RAGE complex with AGEs and Aβ acts on the basis of microglia activity which is phagocytic in nature.

Azeliragon or PF-04494700, an inhibitor of RAGE, can ameliorate sporadic AD and promote neuroprotection by blocking RAGE activation in various cell type. Aging old duration include some oxidative stress that's leads to the formation of AGEs, which activate RAGE together with Aβ in different active cell type either be targeting cells or signaling cells. The process of triggering RAGE towards TXNIP expression, BBB leakage, monocytes infiltration and subsequent inflammation. The inflammatory gene expression promote in the glial cells by the activation of RAGE which enhance the Aβ production in the brain and neurotoxicity. RAGE triggering in neuronal cells induces oxidative stress and the production of M-CSF, leading to inflammation. Thus, main objective of treatments is toaim to inhibit chronic RAGE activation strategies will confer a neuroprotective effects of cell by blocking RAGE-mediated neurovascular dysfunction and stressful pathways.

6.3 Sodium Sulfite and N-Acetylcysteine



Sodium sulfite



N-Acetylcysteine

Sodium sulfite is the soluble sodium salt of sulfurous acid. It is used as a preservative to prevent dried fruits from discolouring, and for preserving meats. Inside the boiler systems, bisulfite and sulfite are the mostly for the prevention

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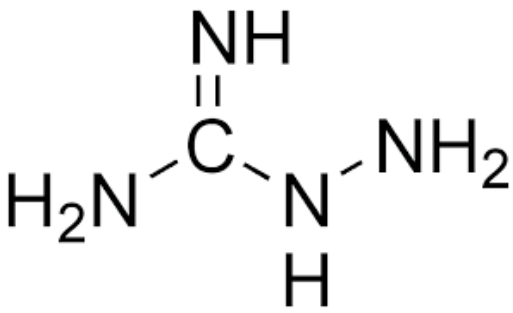
of pitting corrosion that commonly employed oxygen scavengers used, these productsare also a by-product of sulphur-di-oxide scrubbing, which is a part of the flue-gas desulfurization process.

Acetylcysteine, also known as *N*-acetylcysteine (NAC), is a medication that is used in the treatment of paracetamol (acetaminophen) overdose, and to loosen thick mucus in individuals with cystic fibrosis or chronic obstructive pulmonary disease. May be taken by different administer pathways such as intravenous or by vein, by oral, or inhaled as a mist. Some people used it as a dietary nutrient supplement.

The study evaluates the inhibitory effect of various chemicals on the advanced glycation end-product (AGEs) cross-linking caused in protein by glucose degradation products (GDPs). A few organic and inorganic chemicals along with AGE inhibitor, such as Aminoguanidine, for their inhibiting effect were demonstrated(Sakai *et al.*, 2001). Human serum albumin (HAS) or collagen IV (from human placenta) was incubated in phosphate buffer solution with an AGE accelerator (glyoxal, methylglyoxal, 3-deoxyglucosone) with sodium sulphite and N-acetylcysteine at 37°C for 14 days. After a given incubation time, fluorescence intensity [(FI) excitation at 370 nm, measurement at 440 nm) was determined.Sodium sulphite and N-acetylcysteine suppressed the increase in fluorescence intensity seen after incubation of HSA with methylglyoxal. Sodium sulfite and N-acetylcysteine showed significant inhibitory effect on RAGE. We can conclude that, Sodium sulfite and N-acetylcysteine inhibits the RAGE.

6.4 Aminoguanidine(AG)



Structure of Aminoguanidine

Aminoguanidine (AG) is a scavenger of reactive carbonyl groups, especially of dicarbonyl compounds. This activation and overall path may prevent the formation of glycoxidation and lipoxidation products. It can interrupt vicious cycles of oxidative damage. It may inhibit both collagen cross-linking and lipid peroxidation, *in vitro*. It is a prototypic therapeutic agent for the prevention of formation of AGEs. It reacts rapidly with α,β-dicarbonyl compounds such as methylglyoxal, glyoxal, and 3-deoxyglucosone to prevent the formation of AGEs by blocking carbonyl groups on Amadori products, intermediates in AGE production(Chang *et al.*, 2014).

Inhibition of disease mechanisms, particularly vascular complications in experimental diabetes, by AG has proved that accumulation of AGEs is a risk factor for disease progression. AG has other pharmacological activities, inhibition of nitric oxide synthase and semicarbazide-sensitive amine oxidase (SSAO), at pharmacological concentrations achieved *in vivo* for which controls are required in anti-glycation studies. AG is a highly reactive nucleophilic reagent that reacts with many biological molecules (pyridoxal phosphate, pyruvate, glucose, malondialdehyde, and others). The peak plasma concentration of AG in clinical therapy was 50 μM.

This study aims to investigate the modulatory effect of aminoguanidine (AG), in various stages of experimental periodontitis. 36 Sprague-Dawley rats were used. AG was systemically administered in the induction, progression, and recovery phases of ligature-induced periodontitis. Dynamic changes of the periodontium were evaluated by micro-computed tomography, histology, and immunohisto chemistry of the RAGE. This molecular mechanisms (under observation) were evaluated by myeloperoxidase (that's lead inside the neuron cells) activity, gene level expression of RAGE, and markers associated with tissue repair and homeostasis, including vascular endothelial growth factor (VEGF), type I collagen, fibronectin, and periostin. In the induction sites, periodontal bone loss was significantly reduced with inhibition of RAGE. In the progression and recovery sites, similar trends were observed, with

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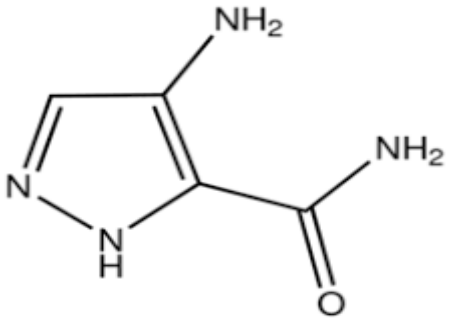
insignificant differences relative to NS-treated animals.AG reduced periodontal bone loss during the induction of experimental periodontitis, and some of the effects that's appeared to be insignificant in the recovery phase and progression phase. It was related to the inhibition of the AGE-RAGE axis to resume cell-matrix interactions and maintain tissue integrity. Hence, we can conclude that Aminoguanidine inhibits the RAGE significantly.

6.5 Pyrazole-5-Carboxamide



Structure of Pyrazole-5-carboxamide

A series of pyrazole-5-carboxamides were designed, synthesized and biologically evaluated to develop novel inhibitors of RAGE for the treatment of Alzheimer's disease(Han *et al.*, 2014).The initial step in the development of novel RAGE inhibitorsaimed on the identification of a new N-heterocyclic scaffold. Usingan Enzyme-linked immunosorbent assay (ELISA), a variety of aryl-substituted N-heterocyclic systems, such as triazoles, quinazolines, triazines and pyridazines were evaluated. To further determine the use of pyrazole-5-carboxamide as a novel scaffold for the development of RAGE inhibitors, a series of 4-chlophenoxy analogs were synthesized and evaluated, which were designed based on some structures of the initially identified RAGE anti/inhibitors. The 4-chlorophenoxy analogs exhibited higher RAGE inhibitory activities than the corresponding methoxy analogs. Based on these results, it was confirmed that apyrazole-5-carboxamide could be used as a scaffold for the development of novel RAGE inhibitors. Analyses of the extensive structure-activity relationship (SAR) led to identify a 4-fluorophenoxy analog (40) that exhibited improved *in vitro* RAGE inhibitory activity and favorable aqueous solubility than the parent 2-aminopyrimidine. The Surface Plasmon Resonance (SPR) and molecular docking study strongly supported the RAGE inhibitory activity of pyrazole-5-carboxamides. For development of novel RAGE inhibitors for use as potentialAD therapeutics, we designed and synthesized a series of pyrazole-5-carboxamides, which were determined to be excellent RAGE inhibitors. We also established the structure activity relationship of the pyrazole-5-carboxamide inhibitors based on their in vitro RAGE inhibition. Based on the *in vitro* activities of the initial pyrazole-5-carboxamide analogs, these results implied that the pyrazolemoiety may act as a hydrogen bonding acceptor or may conceal the free hydrogen inside the pyrazole moiety, which is most crucial for the requisite of RAGE inhibition. Studies of the Ab-lowering effect and aqueous solubility ofpyrazole-5-carboxamides are demonstrated. An acute model study using the representative Pyrazole-5-carboxamideswas performed to determine the contribution of the RAGE inhibitory activity to the desired down-regulation of Ab brain entry after preliminary investigation of *in vivo* exposure. Pyrazole-5-carboxamides was intraperitoneally injected into wild-type mice prior to human Ab injection. Inhibition of Ab brain entry was determined by measuring the amount of human Ab in the brain extracts of the mice. Significant brain Ab-lowering effects without changing the amount of peripheral human Ab was observed. The brain Aβ-lowering effect of 40 has also described. Hence, we can conclude that Pyrazole-5-carboxamides inhibits the Receptor for Advanced Glycation End Products (RAGE).

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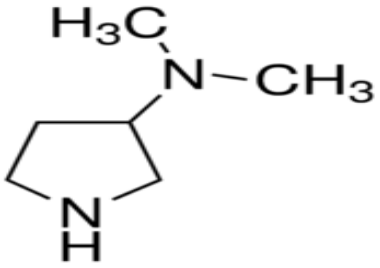
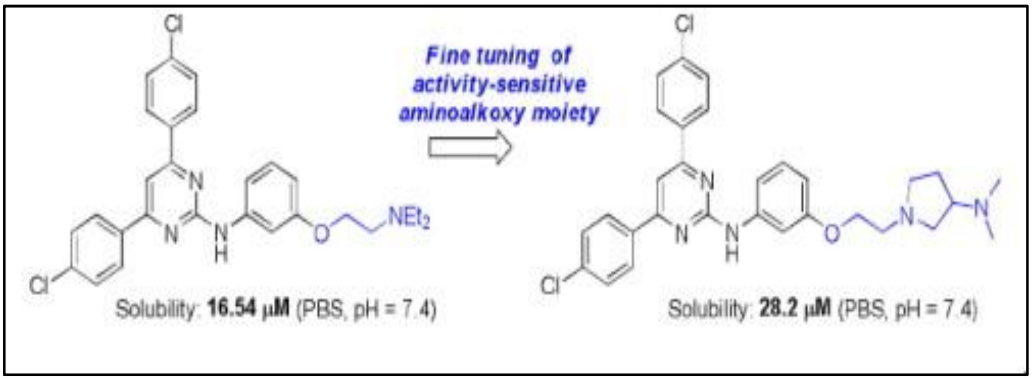
6.6 4,6-Bisphenyl-2-(3-Alkoxyanilino)Pyrimidine and 3-(N,N-Di- Methylamino) Pyrrolidine



Structure of 3-(N,N-dimethylamino) Pyrrolidine

The novel series of 4,6-disubstituted 2-aminopyrimidines as RAGE inhibitors, that demonstrated or created on the structural basis of argpyrimidine. Potent*in vitro* RAGE inhibition was observed in 4,6-bis(4-chlorophenyl)-2-aminopyrimidine, as identified through structure–activity relationship (SAR) studies on the pyrimidine core moiety. It was convinced that the N-aryl linker is crucial for RAGE inhibition(Han *et al.*, 2015).

The inhibitory activities of RAGE of the synthesized analogs were evaluated through ELISAs technique (enzyme-linked immunosorbent assays) using 20 lM of each analogous. The assay results exhibited increased inhibitory activities by 84% and 74%, respectively. These results imply that altering the length or flexibility of the aminoalkoxy moiety sensitively reduced inhibitory activity.



Fine tuning of 4,6-bisphenyl-2-(3-alkoxyanilino)pyrimidine was demonstrated, highlighting on the activity-sensitive aminoalkoxymoiety of 3, a novel RAGE inhibitor. Through analyses of systematic modification studies, it was confirmed that the terminal tertiary amine unit and linker length are important for high RAGE inhibitory activity. In particular, 3-(N,N-dimethylamino) pyrrolidine analog was identified as a therapeutically applicable RAGE inhibitor with improved activity and solubility compared to the parent inhibitor 3. The binding pattern with RAGE predicted via molecular modeling, well supported basis for the improved activity. Extensive research regarding the therapeutic applications is making good progress. For RAGE inhibitory activity, the following reactions were carried out:

1. Mitsunobu reaction
2. Nitro-reduction
3. Microwave-assisted aromatic substitution reaction
4. N-alkylation reaction
5. ELISA test

By the fine tuning of activity of sensitivity of aminoalkoxy moiety of 4,6-bisphenyl-2-(3-alkoxyanilino)pyrimidine as a novel inhibitor (anti activator) of the RAGE, in the last tertiary amine was elucidated as an essential part associated with RAGE inhibition. On the basis of this , a 3-(N,N-dimethylamino)pyrrolidine analog was identified as a therapeutically useful RAGE inhibitor with improved activity and solubility. Molecular modeling studies predicted that the improved inhibitory activity is induced by 4,6-bisphenyl-2-(3-alkoxyanilino) pyrimidine and 3-(N,N-dimethylamino) pyrrolidine at the RAGE binding site.

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6.7 Papavarine

Structure of Papavarine

Papaverine (Latin *papaver*, "poppy") is an opium alkaloid drug, used primarily in the treatment of various diseases. It is found in the opium poppy. Papaverine has different form and regulation form in both pharmacological action from the analgesic (morphine-related) opium alkaloids (opiates) and the structural process.Papaverine hydrochloride (molecular weight, 375.85 Da) was used as a drug for the *in vitro* study(El-Far *et al.*, 2018). *Cell lines.* HT1080 human fibrosarcoma cells were transfected with a plasmid containing human full-length RAGE cDNA or cytoplasmic domain-deleted dnRAGE cDNA, or with the vector alone. Cells were maintained in RPMI-1640 medium supplemented with 10% fetal bovine serum, 100U/ml penicillin and 100 µg/ml streptomycin in the presence of G418.The following aasays were performed:

1. NF-κB luciferase assay,
2. Western blot analysis,
3. Plate-binding assays,
4. Cell proliferation assay,
5. Cell migration assay,
6. Cell invasion assay and
7. Statistical analysis.

Studies evaluate the inhibitory effects of papaverine on the RAGE-dependent NF-κB intracellular signaling pathway. Using the C6 glioma system, which reflected RAGE-dependent NF-κB activity, HMGB-1-induced activation of NF-κB was evaluated in the presence of papaverine in the culture media. HMGB-1 significantly induced intracellular NF-κB activation, however, this up-regulation was inhibited by papaverine treatment (10 or 20 µM). Theincrease in NF-κB activity induced by glyceraldehy de-derived AGE-BSA, another RAGE ligand, was significantly inhibited by papaverine.. The study subsequently confirmed the papaverine-RAGE binding using a plate assay. Papaverine significantly and dose-dependently competed for the binding between glyceraldehyde-derived AGE-BSA and recombinant soluble RAGE , which suggested that the binding site of papaverine to RAGE may be shared with that of AGE-BSA.

The present study identifies papaverine as a RAGE inhibitor using the drug design system COSMOS, an example of drug repositioning, the application of well-known existing drugs and compounds for novel indications.RAGE has been implicated in multiple pathogenic processes, in cancer and numerous other diseases, including diabetes, atherosclerosis, inflammatory and neurodegenerative diseases. Therefore, papaverine and its derivatives could be useful in preventing and treating multiple RAGE-associated diseases.

To conclude, the results of this study suggested that papaverine could inhibit RAGE and provided novel insights into the field of RAGE biology.Papaverine more frequently used or was identified as a RAGE inhibitor using the converting to small molecules through optimized-peptide strategy drug design system. To clarify more understanding of RAGE inhibition by papaverine, *in vivo* animal models should be used in future studies.

6.8 Iridoids

Iridoids are a type of monoterpenoids in the general form of cyclopentanopyran, found in a wide variety of plants and animals. They are biosynthetically derived from 8-oxogeranial. Iridoids are typically found in plants as glycosides, bound to glucose. Iridoids have potential biological activities. The phytochemical constituents in plant-based foods

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exhibit anti-glycation activities, among these phytochemicals are Iridoids.The anti-AGE potential of iridoids has been demonstrated *in vitro* as well as*in vivo*, while revealing possible mechanisms of action(West *et al.*, 2016). Including iridoid food sources in the diet may be a useful component of strategies intended to inhibit RAGE in the body.

In an*in vitro* bovine serum antiglycation assay, a month of daily ingestion of oleuropein by alloxan-induced diabetic wistar rats reduced serum glucose concentrationsand thiobarbituric acid reactive substances (TBARS),a measurement of lipid oxidation products. Oleuropein showed activity upto a concentration of 100 µMwhenribose or fructose were used as the glycating agents. Hydroxytyrosol (reactive molecules), a major metabolite of oleuropein,its binds with methylglyoxal under physiological conditions, thereby limiting the formation of AGEs via carbonyl scavenging. As lipid peroxidation is an important event in certain AGE formation pathways, theantioxidant activity of oleuropein slows AGEformation.

An iridoid rich extract from *Calendula officinalis*(Pot marigold) fruit was fed tostreptozotocin-induced diabetic rats for 12 weeks. Study with diabeticanimals revealed that 12 weeks of *C. officinalis*iridoidglycoside extract consumption reduced fasting blood glucose.Increasing doses of crude extract from *C. officinalis*fruit were fed to different groups of streptozotocin-induceddiabetic wistar rats for 10 days, with comparisons for untreated diabetic and non-diabetic controls. Ingestionof the extract reduced serum glucose and glycosylated protein concentrations. Kidney based AGEs (which is measured byfluorescent instruments), and mitochondrial TBARS were also decreasedby this extract.

Western blot analysis results indicated lower RAGE, NF-kβ, and serum transforming growthfactor β1 (TGF-β1) expression in renal tissue of animalsconsuming the extract, as well as lower carboxymethyl lysine(CML) production.

Therefore, it is concluded that the iridoid glycosidesfrom *C. officinalis* fruit that is mainly inhibited TGF- β1 and ECM which leads to productionby limiting AGE formation.Animal studies with loganin and morroniside indicated thatthese two iridoids control AGE formation *in vitro*. Loganin and morroniside isolated from*C. officinalis* fruit decreased reactive oxygen species production, in rat mesangial cells that had been cultured inthe presence ofAGEs.

Clinical trials with noni juice, amajor dietary source of deacetylasperulosidic acid, provideinsight of a possible antiglycation mechanism of food derivediridoids. Incubation of noni fruit extractreduced glucose-induced bovine eye lens opacity in an *in vitro*cataract model. This extract also inhibited aldose reductaseactivity. Both superoxide dismutaseand catalase inhibit the formation of AGEs. Superoxide removalis a potential mechanism by which iridoids preventAGE formation as well as inhibition of aldose reductase is another anti-AGEmechanism of iridoids.

Gentiana lutea root extract inhibited rat lens and human aldose reductase activity *in vitro*. These types of molecular-docking studies were observed with amarogentin, a secoiridoid found in*G. lutea* root, suggest that it inhibits aldose reductase. Two iridoid glycosides,Demethylmussaenoside and 7-O-acetyl-8-epi-loganic acid, inhibitrabbit lens aldose reductase *in vitro*. reductase.The ability of deacetylasperulosidic acid and loganic acidto directly inhibit *in vitro* glycation of bovine serum albuminby fructose and glucose wasthe finest.

The *in vitro* antioxidant activities of deacetylasperulosidic acidand its β-glucosidase hydrolysis product were evaluated inOxygen Radical Absorbance Capacity (ORAC), α,α-diphenyl-β-picrylhydrazyl (DPPH) radical scavenging and Fe3+ reducing powerassays. All these increased value of antioxidant activity was observed in all3 assays for the hydrolysis product, whereasdeacetylasperulosidic acid had low activity. Theseobservationssuggest that the antioxidant activity of iridoids innoni fruit are greatest.Seven iridoid glycosides displayed no activity, via intraperitonealinjection, against leukemia P388 tumor cells in BDF1 mice.But after treatment with β-glucosidase, survival time improvedwith all but one of the iridoids. The aglyconeof one of these iridoids, scandoside methyl ester, had greater*in vivo* anti-tumor activity than 5-fluorouracil.Therefore, control of AGEaccumulation should be an important component of healthmanagement. Iridoids claimed to have the potential to inhibitthe formation of AGEs. The antiglycation activities of iridoids involve NF-kβ and aldose reductase inhibition,trapping of dicarbonyls, and antioxidant pathways. Infact, there are several antioxidant mechanisms,whereby the oxidation of Amadori products is diminished. It is reasonablyconcluded that Iridoids play a very important role for inhibition of the RAGE.

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6.9 FPS-ZM1

For a novel class of RAGE inhibitors to be generated, 5,000 small molecules were screened for inhibition of interaction of RAGE-Aβ. The lead compounds were identified, about 100 structurally related compounds was screened for RAGE Aβinhibition and ability to cross the BBB. A compound named FPS-ZM1 blocked inflammatory signaling in the mouse brain, reduced Aβ accumulation, and improved cognitive performance(Migliaccio, 2019). Importantly, FPS-ZM1 did not cause toxic side effects in mice, even at doses as high as 500 mg per kg. FPS-ZM1 has been demonstrated in other mouse models of neuropathology. Using a rat model of neuroinflammation with intra-hippocampal injection of AGEs, FPS-ZM1 reduced brain inflammation and Aβproduction and improved cognitive function. In a rat stroke model of intracerebral hemorrhage, FPS-ZM1 reduced the BBB dysfunction and nerve fiber injury associated with early brain injury after stroke. In primary cultured rat microglia, FPS-ZM1 diminished AGE-induced inflammation and reactive oxygen species. In heart failure induced by transverse aortic constriction in mice, eight weeks of FPS-ZM1 administration inhibited cardiac hypertrophy and reduced inflammation in cardiac tissues. In a mouse model of asthma induced by toluene diisocyanate, FPS-ZM1 administration impaired airway reactivity, inflammation, and deviant β-catenin signaling. Most recently, it was demonstrated that small-molecule inhibitors of RAGE including FPS-ZM1 impair cancer progression and metastasis. *In vitro* studies with highly metastatic breast cancer cells revealed that FPS-ZM1 revoked the excess invasion caused by RAGE. No effect was seen on cell viability with FPS-ZM1, suggesting that inhibiting RAGE with FPS-ZM1 affects its migratory and invasive properties. In a mouse xenograft model, intraperitoneal injectionof FPS-ZM1 or vehicle control impaired tumor growth and metastasis to lung and liver, comparedto vehicle treated controls.

6.10 Pioglitazone

Insulin resistance, which may influence Alzheimer's disease, is associated with an increase in circulating AGE sand an enhanced expression of the RAGE. Inhibition of RAGE attenuates the neuronal damage(Liu *et al.*, 2010). Specific ligands for peroxisome proliferator-activated receptor γ (PPARγ), which are effective in animal models of Alzheimer's disease and other neuro inflammatory diseases, have been shown to inhibit RAGE expression. It was investigated that the effect of PPARγ agonist, pioglitazone, oncognition function of the RAGE system in a rodent model of insulin resistance, thefructose-drinking rats. Six-week-old male Wistar rats were fed a standard commercial diet and water withor without 10% fructose for 16 weeks. The animals were divided into 4 groups; non-treated and water-drinking rats (control group); and water-drinking (control treatment group); pioglitazonetreated, non-treated and fructose-drinking rats (fructosegroup) and fructose-drinking rats (fructose treatment group). Pioglitazone was given at the dose of 10 mg/kg d by gavage for the last 12 weeks of the 16-week period. The results demonstrated that pioglitazone treatment reduced the escape latency in Morris water maze test, inhibited the RAGE expression in the cerebral cortex of fructose-drinking rats. These findings conclude that, the activation of RAGE system contributes to the brain damage of insulin resistance. Pioglitazone administration can improve cognition function probably related to its effect of decreasing the activation of RAGE system, which correlates with block of NAPDH oxidase and NF-κ Bactivation in this rodent model of insulin resistance. The protein expressions of RAGE in fructose-drinking rats was down regulated with pioglitazone treatment. Involvement of RAGE by AGEs stimulates the generation of oxidative stress, subsequently modulating the expression of reactive-oxygen-species related signal events. These reactive oxygen intermediates and associated signal events have attributed to the activation of NADPH oxidase (Wautier et al., 2001). The results showed increased levels of NADPH oxidase and NF-κB expression infructose-drinking rats, indicating that oxidative stress and NF-κBactivation contribute to cerebral tissues impairment. NF-κB activation increases the expression of a large number of pro-inflammatory cytokines including TNFα and IL-1β trigger inflammatory cascade that causes tissue damage (Kuhad et al., 2009). Indeed, the levels of TNFα and IL-1β expression in fructosedrinkingrats increased compared to control rats. ioglitazone, an insulin sensitizer, is a synthetic ligand of PPAR γ reported to down regulate RAGE expression in vitro and in vivo (Yoshidaet al, 2006;Wang et al, 2006; Duan et al, 2009). Treatment with pioglita zone effectively reduced phospho-NF-κB p65expression and inflammatory cytokines production. Therefore, to improve insulin resistance, pioglitazone can reduce the deposition of AGEs in the brain and the expression of RAGE, inhibitoxidative

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stress and lower the production of inflammatory cytokines. In conclusion, the present study suggest that the activity of AGEs–RAGE pathway, NADPH oxidase and NF-κB in brain increased in high fructose-drinking rats, which may contribute to brain impairment of this animal model of insulin resistance. Pioglitazone administration reversed this increase and enhanced performance in Morris water maze besides increasing insulin sensitivity, subsequently, decreasing the formation of AGEs and inhibition of RAGE, thus inhibiting oxidative stress and inflammatory reactions. This provides a theoretical basis for applying pioglitazone prior in the protection and treatment of the brain injury in insulin resistance and other related diseases.

6.11 Irbesatan

It was investigated that, Irbesartan could inhibit the RAGE gene expression in tubular cells. Irbesartan could significantly block the RAGE and mRNA levels intubular cells AGEs exert pleiotropic actions on various types of cells by inducing the generation of intracellular reactive oxygen species (ROS)through the interaction with cell surface receptor, RAGE. Incubation with AGE-BSA for 24 h increased ROS generation by about 1.4-fold,which was blocked by the treatment with irbesartan(Matsui *et al.*, 2010).24-h treatment with AGE-BSA induced apoptotic cell death of tubular cells, which were inhibited by irbesartan. This drug was also found to inhibit the AGE-induced upregulationm RNA levels in tubular cells. TGF over production by AGE-exposed tubular cellswas also blocked by the treatment with irbesartan. In this study, it was clearly demonstrated for that irbesartan,an Angiotensin Receptor Blocker drug inhibited the RAGE, apoptosis and inflammatory, thrombogenic and fibrogenic gene expressions and TGF gene expressions), and also the TGF production in cultured human proximal tubular cells probably by suppressing RAGE levels and subsequent ROS generation. Blockade of the Renin-Angiotens in System by Irbesartan may play a protective role against tubular injury in diabetes by diminishing the deleterious effects of AGEs by down-regulation of RAGE. These observations suggest that BP lowering-independent renal protective effects of irbesartan observed in type 2 diabetic patient could be attributed to the RAGE axis by its blocking property. The peak plasma concentration of irbesartan is observed. So, the concentration of irbesartan having beneficial effects on tubular cells used in the present experiments (1Molar) may also be comparable to the therapeutic levels which are achieved in the treatments for patients with hypertension. In the present study, it was found that irbesartan treatment for 4 h significantly inhibited the RAGE and mRNA levels in tubular cells. These findings suggest that RAGE suppressionis the primary target for the anti-oxidative, anti-apoptotic, anti-inflammatory, anti-thrombogenic and anti-fibrogenic effects of irbesartan on proximal tubular cells. Therefore, it is clarified that, the molecular mechanisms are precise, in which the drug irbesartan inhibits the RAGE expression in tubular cells. Irbesartan may also reduce mRNA levels in AGE-exposed tubular cells by blocking the endogenous angiotensin II actions as it has been previously found that angiotensin II itself up-regulates RAGE mRNA levels inendothelial cells and vascular pericytes. This provides a novel beneficial aspect of irbesartan on diabetic nephropathy. It can function as an agent for inhibiting the RAGE and can play a protective role in the treatment of diabetic nephropathy.

6.12 Tranilast

The S100 protein family is one of the ligands of RAGE. The binding of one site of S100A11 dimer to RAGE V domain brings about homodimerization of two adjacent RAGEs and auto phosphorylation of their cytoplasmic domains. This autophosphorylation triggers a series of signal transduction cascades, leads to cell proliferation and survival. The interactions between mS100A11 and RAGE V domain were characterized by using techniques such as fluorescence spectroscopy and NMR spectroscopy(Huang, Chou and Yu, 2016). The NMR titration experiments and plotting bar diagrams identified the residues of binding sites of mS100A11 homodimer and RAGE V domain. Mapping the residues on 3D structures elucidates the binding sites between mS100A11 and RAGE V domain. According to the experimental results, it was demonstrated that the binding sites between mS100A11 and the RAGEV domain. This region is similar to the regions that were the binding interfaces of other S100 family proteins complexes with the RAGE V domain. For instance, S100P homodimer interacts with the RAGE V domain by helix 1 of one monomer and helix 4 of another monomer. The binding site ofS100A6 to the RAGE V domain is located at loops 1 and 3 and helix 4. For S100B, the

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binding region on loop 1, loop 3, helix 3, and helix 4 was investigated to determine its interaction with the RAGE V domain. These S100 proteins have similar regions in binding interfaces because of their high structural similarity in three dimensions. Some parts of the minor differences in binding sites between each S100 protein and the RAGE V domain results from distinct identification of RAGE V domain with S100 proteins due to the differences in the hydrophobic region, polarity, net charge, or properties of S100 proteins. Overall, the results reveal that theS100A11 homodimer interacts with two RAGE V domain molecules symmetrically and forms a hetero-tetrameric complex model. This model of S100A11-RAGE V domain complex would be useful for designing drugs to block the interaction between mS100A11 and the RAGE V domain.

The tranilast molecule proved to be a potential drug for blocking the interaction between mS100A11 and the RAGEV domain based on the results of experiments, including fluorescence, NMR and WST-1 cell proliferation assays. Figure below shows the overlap of the following two complexes that were generated by our HADDOCK results:-

1. S100A11-RAGE V domain complex, shown in *green*, and
2. S100A11-tranilast complex (S100A11 is shown in *green)*, and
3. Tranilast molecules are shown in *multicolor*.

This clearly shows that tranilast blocked the binding sites between mS100A11 and the RAGE V domain. These findings give prominence to the inhibition of cell proliferation resulting from the blocking interaction of S100A11 with RAGE using the tranilast molecule. This will also be helpful for improving therapeutic strategies to treat RAGE-dependent diseases and probably cancer also.

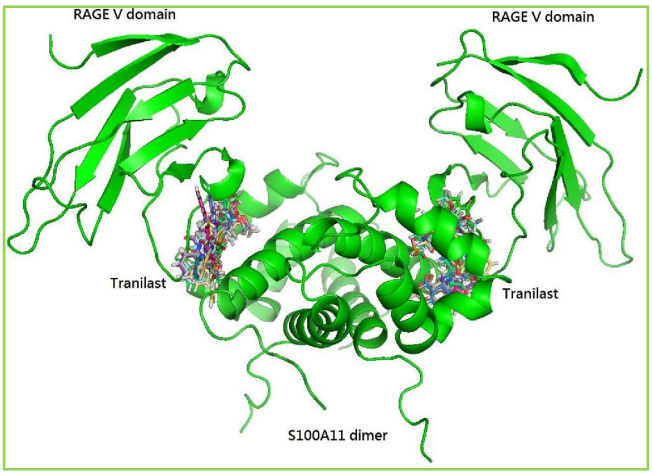

Figure: Superimposition of two complex structures (S100A11-RAGE V domain and S100A11-tranilast). The S100A11-RAGE V domain complex isshown in green, and tranilast molecules are shown in multicolour. Tranilast blocks the interaction between mS100A11 and the RAGE V domain.

6.13 TTP488

TTP488 is an orally bio available small-molecule inhibitor of RAGE. The majority of information on TTP488 comprises human clinical studies. Preclinical *in vitro* and mouse model studies have been hampered by the lack of commercial availability of TTP488. Although most preclinical studies on RAGE have focused on diabetic complications, cardiovascular diseases and cancer, the majority of clinical trial work with TTP488 has been in AD cohorts. TTP488 inhibits binding of multiple RAGE ligands, including AGEs, HMGB1, S100B and Aβ. In a mouse model of AD, TTP488 administration inhibited inflammatory signaling, neuronal Aβ accumulation, and neurocognitive function. A phase II double-blind trialin mild to moderate AD focused on the safety of TTP488. In 2007, 18-month phase II trial was carried out 399 mild to moderate AD subjects to a low-dose, high-dose, or placebo group. The study was discontinued at six months as the high-dose group displayed worsening cognitive measures. A follow-up analysis of the low-dose group showed a clinical benefit of slowing cognitive decline. As a result, a phase III trial is currently in

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a mild AD cohort of 800 subjects. Various groups have developed new TTP488 derivatives by modifying the imidazole ring, the hydrophobic side groups, and the aromatic core. These studies have shown the amino alkyl linker is necessary for effective inhibition of RAGE ligand binding and signaling. Most studies testing derivatives of TTP488 have been performed in preclinical models of AD, where inhibition of disease was also observed.

6.14 PF-04494700

RAGE has been associated in the pathophysiology of Alzheimer'sdisease (AD). Cells expressing RAGE are activated in the plaque. Antagonism of RAGE ligand interactions, using either asoluble RAGE antagonist or an anti-RAGE antibody, reduces amyloidplaque formation in mice models. A 10-week,phase II, double-blind, randomized, placebo-controlled, multicentre trial of PF-04494700, an orally bio available soluble RAGE antagonist, in patients with mild to moderate AD, was demonstrated(Marwan N. Sabbagh1, 2012). Subjects aged50 years who met NINCDS-ADRDA criteria for AD of mild tomoderate severity were randomized to low-dose PF-04494700 (30 mg/day for 6 days and later, 10 mg/day for 63 days), high-dose PF-04494700 (60mg/day for 6 days and then 20 mg/day for 63 days).The primary objective is to evaluate the safety and efficacy ofPF-04494700. Safety evaluations included adverse events, laboratorytests, vital signs, 12-lead electrocardiogram(ECG) and 24-hour 12-lead serial ECG. Secondary endpoints includedeffects of PF-04494700 on surrogate plasma efficacy markers and cognitive function, and determining its pharmacokinetic profile.T here were no clinically relevant between-group differences in baseline demographic or clinical characteristics. Mean age was between groups (PF-04494700: 75.6years, placebo: 74.1 years). Subjects receiving PF-04494700 60/20mg, 32% experienced an the adverse events judged by the investigator to be treatment related v/s 44% treated with PF-04494700 30/10 mg, and 50% of subjects receiving placebo. Both dosing regimens of PF-04494700 were safe and well-tolerated in patients with mild to moderate AD over 10 weeks. The overall incidence of treatment related AEs was similar for PF-04494700 and placebo. PF-04494700 is safe and well-tolerated as a potential treatment for AD.

VII. CONCLUSION

We can conclude that, for the Receptor for Advanced Glycation End-products (RAGE), there are a variety of natural as well as synthetic advanced glycation end-products inhibitors. These are either AGE-breakers or have their anti-glycation activity as evaluated either by *in vitro* or *in vivo* study protocols. TheNaturalRAGE inhibitors of Marine sources are Silymarin (*Silybum marianum*) and Scalarin (*Eurypongia rosea*). Herbal sources are Rosemary(carnosic acid) , Hyperoside (St. John's wort) and Yerba mate (*Ilex paraguariensis*). Certain food sources that inhibit the RAGE are Resveratrol (from the skin of grapes), Vitamin A (Retinol), Quercetin (from apples, red raspberries, grapes and onions), Tomato paste fraction (Rutin), Sweet potato, Edible Mushroom (*Lactarius deterrimus*) and Chestnuts (*Castanea sativa*). Whereas, the synthetic sources are Aminoguanidine, Azeliragon (or PF-04494700), Heparin, Pyrazole-5-carboxamide, Papavarine, Sodium sulfite, N-acetylcysteine,4,6-bisphenyl-2-(3-alkoxyanilino) pyrimidine, 3-(N,N-dimethylamino) pyrrolidine, Pioglitazone, FPS ZM1, Irbesartan, Tranilast, TTP488, PF04494700 and certain Iridoids. Consequently, the quest for new AGE inhibitors is considered of paramount importance which can be of therapeutic potential in patients with diabetes, Alzheimer's or other age-related diseases. Practical implications are focused on studies for inhibition of AGE formation which have received a great recognition nowadays. Inhibition of RAGE and prevention in the formation of AGE is believed to play a key role in the prevention of diabetic and cardiovascular complications. Investigation of nutritional bioactive compounds with anti-glycation properties provides future scope for prevention or intervention related to AGEs complications. Strategies to limit new AGE formation should be developed or enhanced in order to limit AGEs intake. Therefore, inhibition of RAGE and formation of AGE restriction, represents a relatively a simple strategy to preserve healthy status and possibly supports the pharmacological treatment for certain age-related disease like diabetes, alzheimer's and renal diseases. Thus, Inhibition of RAGE becomes crucial and it can be accomplished by, Natural as well as Synthetic Sources Receptor for Advanced Glycation End-products (RAGE) Inhibitors, for a well-being and a healthy lifestyle.

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REFERENCES (BIBLIOGRAPHY)

[1]. Alhusban, A., Alkhazaleh, E. and El-Elimat, T. (2017) 'Silymarin Ameliorates Diabetes-Induced Proangiogenic Response in Brain Endothelial Cells through a GSK-3 β Inhibition-Induced Reduction of VEGF Release', Journal of Diabetes Research. doi: 10.1155/2017/2537216.

[2]. Burstein, A. H. et al. (2018) 'Slowing of Loss of Cognition in Mild Alzheimer ' s Disease', The Journal of Prevention of Alzheimer's Disease, 5(2), pp. 149–154.

[3]. Buttari, B. et al. (2013) 'Resveratrol prevents dendritic cell maturation in response to advanced glycation end products', Oxidative Medicine and Cellular Longevity, 2013. doi: 10.1155/2013/574029.

[4]. Chang, P.-C. et al. (2014) 'Aminoguanidine Inhibits the AGE–RAGE Axis to Modulate the Induction of Periodontitis but Has Limited Effects on the Progression and Recovery of Experimental Periodontitis: A Preliminary Study', Journal of Periodontology, pp. 729–739. doi: 10.1902/jop.2013.130238.

[5]. El-Far, A. H. A. M. et al. (2018) 'In vitro anticancer effects of a RAGE inhibitor discovered using a structure-based drug design system', Oncology Letters, 15(4), pp. 4627–4634. doi: 10.3892/ol.2018.7902.

[6]. Gelain, D. P. et al. (2011) 'Vitamin A (retinol) up-regulates the receptor for advanced glycation endproducts (RAGE) through p38 and Akt oxidant-dependent activation', Toxicology. Elsevier Ireland Ltd, 289(1), pp. 38–44. doi: 10.1016/j.tox.2011.07.008.

[7]. Guzmán, E. A. et al. (2019) 'The marine natural product Scalarin inhibits the receptor for advanced glycation end products (RAGE) and autophagy in the PANC-1 and MIA PaCa-2 pancreatic cancer cell lines', Investigational New Drugs. Investigational New Drugs, 37(2), pp. 262–270. doi: 10.1007/s10637-018-0635-4.

[8]. Han, Y. T. et al. (2014) 'Pyrazole-5-carboxamides, novel inhibitors of receptor for advanced glycation end products (RAGE)', European Journal of Medicinal Chemistry. Elsevier Masson SAS, 79, pp. 128–142. doi: 10.1016/j.ejmech.2014.03.072.

[9]. Han, Y. T. et al. (2015) 'Fine tuning of 4,6-bisphenyl-2-(3-alkoxyanilino)pyrimidine focusing on the activity-sensitive aminoalkoxy moiety for a therapeutically useful inhibitor of receptor for advanced glycation end products (RAGE)', Bioorganic and Medicinal Chemistry. Elsevier Ltd, 23(3), pp. 579–587. doi: 10.1016/j.bmc.2014.12.003.

[10]. Huang, Y., Chou, R. and Yu, C. (2016) 'Tranilast Blocks the Interaction between the Protein S100A11 and Receptor for Advanced Glycation End Products (RAGE) V Domain and Inhibits Cell Proliferation *', 291(27), pp. 14300–14310. doi: 10.1074/jbc.M116.722215.

[11]. Jedsadayanmata, A. (2005) 'In Vitro Antiglycation Activity of Arbutin', Naresuan University Journal, 13(2), pp. 35–41.

[12]. Kiho, T. et al. (2014) 'Tomato Paste Fraction Inhibiting the Formation of Advanced Glycation End-products', 8451(May). doi: 10.1271/bbb.68.200.

[13]. Lan, C. Y. et al. (2019) 'Quercetin facilitates cell death and chemosensitivity through RAGE/PI3K/AKT/mTOR axis in human pancreatic cancer cells', Journal of Food and Drug Analysis. Elsevier Ltd, 27(4), pp. 887–896. doi: 10.1016/j.jfda.2019.07.001.

[14]. Liu, X. et al. (2010) 'Effect of pioglitazone on insulin resistance in fructose-drinking rats correlates with AGEs/RAGE inhibition and block of NAPDH oxidase and NF kappa B activation', European Journal of Pharmacology. Elsevier B.V., 629(1–3), pp. 153–158. doi: 10.1016/j.ejphar.2009.11.059.

[15]. Lunceford, N. and Gugliucci, A. (2005) 'Ilex paraguariensis extracts inhibit AGE formation more efficiently than green tea', Fitoterapia, pp. 419–427. doi: 10.1016/j.fitote.2005.03.021.

[16]. Marwan N. Sabbagh1, Joanne Bell2, Albert Agro3, P. A., Douglas Galasko5, 1Sun Health Research Institute, Sun City, AZ, USA; 2Pfizer Global Research and Development, Groton, CT, USA; 3TransTech Pharma, Inc., High Point, NC, U. 4Georgetown and University Medical Center, Washington, DC, U. (2012) 'An Oral Antagonist Of The Receptor (Rage) Is Safe And Well-Tolerated In The Treatment Of Alzheimer ' S Disease : Utility Of Plasma Exchange With Five Percent Human Albumin Grifols ® In The Treatment Of

IJARSCT
ISSN (Online) 2581-9429
International Journal of Advanced Research in Science, Communication and Technology (IJARSCT)
Volume 2, Issue 1, December 2022
Impact Factor: 6.252

Alzheimer ' S Disease : Functional Imaging (SPECT', p. 788.

[17]. Matsui, T. et al. (2010) 'Irbesartan inhibits advanced glycation end product (AGE)-induced proximal tubular cell injury in vitro by suppressing receptor for AGEs (RAGE) expression', Pharmacological Research, 61(1), pp. 34–39. doi: 10.1016/j.phrs.2009.07.004.

[18]. Migliaccio, A. R. (2019) 'Receptor for Advanced Glycation End Products Antagonism Blunts Kidney Damage in Transgenic Townes Sickle Mice', 10(July). doi: 10.3389/fphys.2019.00880.

[19]. Ramasamy, R. et al. (2008) 'Receptor for advanced glycation end products - Fundamental roles in the inflammatory response: Winding the way to the pathogenesis of endothelial dysfunction and atherosclerosis', Annals of the New York Academy of Sciences, 1126, pp. 7–13. doi: 10.1196/annals.1433.056.

[20]. Ramkissoon, J. S. et al. (2012) 'Natural inhibitors of advanced glycation end-products', Nutrition and Food Science, 42(6), pp. 397–404. doi: 10.1108/00346651211277645.

[21]. Sadowska-Bartosz, I. and Bartosz, G. (2015) 'Prevention of protein glycation by natural compounds', Molecules, 20(2), pp. 3309–3334. doi: 10.3390/molecules20023309.

[22]. Sakai, A. et al. (2001) 'Sodium sulfite and N-acetylcysteine: new additives to dialysate for inhibiting formation of glucose degradation products and advanced glycation end-products.', Advances in peritoneal dialysis. Conference on Peritoneal Dialysis, pp. 66–70.

[23]. West, B. J. et al. (2016) 'Iridoids are natural glycation inhibitors', Glycoconjugate Journal. Glycoconjugate Journal, 33(4), pp. 671–681. doi: 10.1007/s10719-016-9695-x.

[24]. Wu, C. H. et al. (2011) 'Inhibition of advanced glycation endproduct formation by foodstuffs', Food and Function, 2(5), pp. 224–234. doi: 10.1039/c1fo10026b.

[25]. Zhao, Y. et al. (2015) 'Carnosic Acid as a Major Bioactive Component in Rosemary Extract Ameliorates High-Fat-Diet-Induced Obesity and Metabolic Syndrome in Mice', Journal of Agricultural and Food Chemistry, 63(19), pp. 4843–4852. doi: 10.1021/acs.jafc.5b01246.