International Journal of Science and Research (IJSR)
ISSN: 2319-7064
Impact Factor 2024: 2.102

A New Approach Towards Cancer Cures: Salicylic Acids and its Derivatives

Sarah Agarwal

Abstract: ***Salicylic acid is a known component of various cosmetic products and forms the backbone of the cosmetic industry. Studies have shown that apart from functioning as a peeling agent, multiple derivatives have varied roles. Aspirin, a well - known derivative of SA is a known analgesic and is widely used by hospitals and individuals to overcome pain. Salicylic acid has been found to reduce the neurotoxic effects caused by cancer in patients. Awareness and understanding about the property of salicylic acid is a must. Many people around the world have been using it without understanding what concentrations can be useful. Our studies have tried to understand what is known to the common man about salicylic acid and its derivatives. Through our studies we plan to create an understanding about salicylic acid and its derivatives not just as a medicinal or cosmetic component but as a potential cure for dreaded diseases such a s cancer and neurodegenerative disorders. Even though this research is under trials, making people aware is the need of the day and understanding the background information of the product and society in relation is a must. With further research, our study envisions that cancer death rates could be reduced in large numbers around the world, even without the development of any unique expensive treatments.***

Keywords: Salicylic acid, Aspirin, Cosmetic products, Cancer research, Neurodegenerative disorder, Cyclin - dependent Kinases, Cyclooxygenase

1. Introduction

Salicylic acid and its role

Salicylates are obtained through deacetylation of aspirin (pharmacological intervention) which is in the form acetylsalicylic acid, it is the primary metabolite of aspirin. In the metabolic process, 10% remains unchanged, while the other 90% undergoes various metabolism pathways to form different metabolites including salicylic acid and gentisic acid [1].

Due to salicylic acid's comedolytic property and the ability to exfoliate the stratum corneum, it is considered to be a good peeling agent. Salicylic acid is now considered to be a good desmolytic agent due to its ability to disrupt cellular junctions instead of being presented as a keratolytic agent as it doesn't particularly break or lyse intercellular keratin filaments. Since it belongs to the hydroxy acids group, it has various properties and is widely used in cosmetic dermatology. Salicylic acid has distinct chemical properties to alpha and beta hydroxy groups. Unlike a beta hydroxy acid, it has a carboxyl and hydroxyl group directly attached to an aromatic benzene ring; the hydroxyl group has acidic properties instead of neutral; miscible with epidermal lipids and sebaceous gland lipids in hair follicles because it is lipid soluble. Salicylic acid, an organic acid, is used in skin chemical peeling because of its anti - hyperplastic effect on the epidermis. It has various properties ranging from antimicrobial and antifungal to having an anesthetic effect as prominent as seen through patients' increased ability to tolerate the chemical peeling procedure. Furthermore, this lipophilic agent can extensively reduce sebum secretion in acne patients. In addition, it decreases adhesion of corneocyte cells leading to their loosening and detachment. It can also extract desmosal proteins such as desmogleins, which affects cohesion of epidermal cells, resulting in exfoliation as the cohesion of epidermal cells is lost. Apart from this, it alters underlying dermal tissues and thin the corneal layer without directly wounding the skin or changing epidermic thickness. Although it's suitable to all ethnic groups and skin types of Fitzpatric (I - VI), its restricted in certain conditions including acute viral infection, skin malignancy, tanned skin and active dermatitis at the site [2].

Use of salicylic acid and application of chemical peeling can result in a variety of issues such as the presentation of prolonged erythema in a small proportion of acne vulgaris patients, but this can be treated by applying topical moisturizers. It also results in intense exfoliation and crusting but this eventually settles within the span of 7 - 10 days without causing any permanent damage. Although relatively safe, a very small proportion of dark ethnic groups may suffer from mild symptoms ranging from hyperpigmentation to hypopigmentation and temporary crusting to temporary dryness. Salicysm also poses to be a huge concern which may be due to the immediate absorption when applied topically on the skin and then the rate can be increased by pairing it up with a hydrophilic base or kept under occlusion. Cutaneous absorption can potentially result in an extremely serious, yet rare concern known as systemic toxicity. Apart from this, salicylates can be toxic to the CNS in high concentrations, and this can be manifested through a range of symptoms including nausea, psychosis and dizziness, eventually leading to coma and death. Tinnitus - like symptoms may emerge as a result of increased labyrinthine pressure and there is always a risk of metabolic acidosis in infants and children. Additionally, the respiratory system is affected such as the stimulation of the respiratory centre in the medulla causing hyperventilation and eventually respiratory alkalosis. Salicylates also pose to be toxic when its concentration exceeds by 35 mg/dL in the blood which can be due to various reasons including the application of 20% SA on over 50% body surface area. However, since chemical peeling only uses 30% formulation, it's not risky. Certain groups of patients must also be cautious. For instance, uremic patients are more vulnerable in suffering from hypoglycemia post systemic absorption of salicylate because "these patients have reduced protein binding of salicylate" so the "free form in the blood increases". Some may also suffer with contact allergy, but this can be due to other components involved in the complete procedure of chemical peeling apart from salicylic acid. Unlike α - hydroxy acid peels which belong to category B, thus safe, SA peels are highly discouraged in pregnant patients as it belongs to

category C and has a similar structure to aspirin that can cause miscarriage, birth defects and salicylism [3].

Derivatives of Salicylic acid

Aspirin

Aspirin is a medication used for a variety of illnesses including inflammation, fever, pain, and for its antiplatelet properties through the inhibition of COX (acetylation - mediated inactivation). Salicylic acid, however, is the hydrolyzed form of aspirin, and its derivatives and metabolites can be produced through fruits and vegetables. Different salicylic acid derivatives interact with different derivatives of CDK (CDK is a salicylic acid binding protein), which is a cell cycle regulating protein. It has been found to have analgesic and antipyretic properties and functions through irreversible inhibition of prostaglandin synthesis. Studies have found that chemical peeling with SA in polyethylene glycol helps to reduce and prevent ultraviolet B - induced skin tumors in hairless mice. Also, a risk of salicylism is low in humans with intact skin during chemical peeling using the formulation of SA 30% in polyethylene glycol [4].

Salicyl - carnosine

Salicyl - carnosine is a derivative of ASA and carnosine, and it is synthesised by the condensation of the 2 compounds, coupling antiplatelet agent ASA with a natural antioxidant L - carnosine. These 3 compounds have various effects on the body. For example, "SC has inhibited platelet aggregation more effectively compared to carnosine and was comparable in effectiveness with ASA and another antiplatelet agent ticlopidine". Carnosine ensures that platelet aggregation remains within a constant range and prevents the development of gastric ulceration and erosion, while ASA can induce this. ASA also causes the development of gastric ulceration and erosion. Within 15 - 20 mins, ASA is converted into SA by deacetylation, resulting in an anti - inflammatory, antipyretic and an analgesic effect. Furthermore, after oral administrations, all NSAIDs, including ASA, have poor local and systemic effects on the GI tract mucous membrane, affecting the liver and kidney functions. However, ASA side effects can be reduced, and effectiveness can be increased by producing numerous derivatives of SA. SC has substantially retained its pharmacological properties of its precursors while lacking the detrimental side effects of ASA. SC is also resistant to specific hydrolysis by serum and tissue carnosinase. Superoxide scavengers: superoxide is a compound that contains the superoxide ion, which has the chemical formula O2. Cu/Zn - SOD carries Cu and Zn in its active center, playing a vital role in the antioxidant effect of this dipeptide in vivo. Polymorphonuclear leukocytes are cells that produce reactive oxygen metabolites once stimulated, whilst an increased consumption of molecular oxygen enhances this effect. NSAIDs and antioxidants are used to treat chronic anti - inflammatory conditions as they "are able to react directly with these metabolites or to inhibit their generation in the respiratory burst by specific mechanisms, in addition to NSAIDs classical inhibition of cyclooxygenase [5] [6].

Salicylic acid and Cancer

Aspirin is already known to prevent cardiovascular and cerebrovascular disease, but it can potentially also affect cancer. A study shows that long - term aspirin administration (consumption for 5+ years and between 75 mg to 250 mg) demonstrates a statistically significant positive correlation with cancer prevention, especially in colorectal, pancreatic and prostate cancer, as well as have a possible protective effect in stomach, esophageal, hepatocellular carcinoma, breast, lung, and bronchial. Aspirin reduces the risk of pancreatic cancer by "inhibiting proliferation and stimulating pancreatic cancer cell apoptosis by inactivating the P13K/Akt/mTOR signaling pathway". It furthermore reduces the risk of prostate cancer by "by reducing MMP - 9 activity and uPA expression and decreasing IKK - β - mediated NF - kB activation" to "suppress prostate cancer cell invasion". However, correlation between lymphoma and aspirin remains ambiguous and requires further research in order to draw a conclusive statement. Furthermore, aspirin demonstrates a chemoprotective effect. Although aspirin has an effect on cancer, various factors including age, smoking, alcohol consumption, diabetes and obesity can have a significant impact [7].

Another study has shown that out of various salicylic acid metabolites and their derivatives, the ones with a DHBA compound with a common - OH group at the 2nd carbon inhibit CDK enzyme activity to varying degrees by binding to the same pocket in CDK1. Asp146 and Lyss33 have the ability to inhibit CDK1 based on the interacting functional groups and the orientation at the binding pocket which ultimately affects CDK1's conformation and activity. Moreover, because Asp146 and Lys33 are conserved across several CDK family members and constitute an integral portion of the enzyme's active site, salicylic acid interacts with CDK1 through these amino acids. Apart from this, salicylic acid has the ability to bind to a number of cellular proteins such as IKK, AMP, GAPDH and CDK - 2. Although further research is required regarding the mechanism involved in aspirin reducing the risk of cancer, it is considered to be the most effective against CRC. Aspirin mediated inhibition of COX - 1 causes the prevention of CRC with sequential steps involving COX - 1 and COX - 2. Aspirin and salicylic acid can be absorbed in the intestinal and the colonel epithelial cells, especially if it's an enteric coated tablet which is designed to resist dissolution in the acidic stomach environment. This is followed by its metabolization in the liver. Since it's too hydrophilic, it eventually accumulates within these cells to finally inhibit CDK and present anticancer effects. Meanwhile, it can also be generated through the GI microflora or intracellularly within colonic epithelial cells [4] [8].

A study on breast cancer showed the Antimetastatic effect of low dose aspirin in early intravascular phase of metastasis of breast cancer. Aspirin induces a complex pattern of change in the eicosanoid profile. Other effects of ASA included decrease platelet TXB2 production, thrombin - induced platelet reactivity remains constant, Same number of metastases in the lungs, Infiltration of lung parenchyma by inflammatory cells increased, higher G - CSF + serotonin concentrations in the lungs increased too → so a more pro - inflammatory environment, Increased platelet count,

Increased granulocyte count, decreased systemic NO bioavailability, increased markers of systemic oxidant stress" such as NO deficiency, reduced GSH concentration and increased GSSG concentration, High ASA dose inhibits both isoforms of COX. Salicylic acid is the principal metabolite of aspirin, therefore responsible for its anticancer properties in addition to dietary salicylates [9]. All salicylates including aspirin specifically share the anti - platelet action. Salicylic acid is responsible for aspirin's anti - inflammatory action. Additionally, this compound has a major responsibility in the "development of local and systemic disease resistance to pathogen infection in plants". With a similar property to NSAID, aspirin has the ability to reduce the chances of colorectal cancer by 40%. More specifically, it has the ability to reduce the risk of colorectal adenoma and carcinoma in which it has the ability to inhibit "chemical-induced colonic carcinogenesis". The inflammatory process is involved in "carcinogenesis and cancer growth" therefore salicylates effect on this process indirectly gives it its anticancer properties. This links with the 2 enzymes of COX in which COX 1 converts arachidonic acid into prostaglandins, contributing to the inflammatory response while COX 2 is induced by various growth factors and is associated with tumor progression. On a side note, NSAIDs too inhibit the COX - 2 activity. COx - 2 gene induction takes place in numerous cases such as esophageal and gastric cancers; monocytes, macrophages and fibroblasts; and cells associated with atherosclerosis. Salicylic acid exerts its anti - inflammatory action by preventing the transcription of the COX - 2 gene by at least 50%. In plants, on the other hand, salicylic acid increases "defense gene expression, enhance cell death and alter the expression or activity of various enzymes" to achieve "containment of infection, activation of cell death and induction of local and systemic disease resistance". Limitations in various studies include the restrictions involved in the use of urinary analysis (issues arise in terms of urinary salicylate concentrations, excessive metabolization, urinary pH and flow), effect of dietary salicylate intake and salicylate drugs. Further areas of research include the optimal aspirin dose to produce a chemoprotective effect, ideal baseline, choosing an ideal dietary plant which is continuously affected by pathogen attacks and deciding upon the overall diet [10].

Although Paclitaxel (PAC) and cisplatin (CIS) are used to treat various solid tumors, its limitation is restricted due to its substantial neurotoxic effect as they inhibit cell viability on neuron cells according to MTT ([3 - (4, 5 - dimethylthiazol - 2 - yl) - 2, 5 - diphenyltetrazolium bromide) assay which is used in its detection. PAC "exposure caused a decrease of cell viability and an increase in the ratio of apoptotic cells in dorsal root ganglion (DRG) neurons". CIS induced lipid peroxidation and reduced potency of the antioxidant defense system. Moreover, due to its antioxidant effect, salicylic acid has an effect against the toxicity caused by both these medicines, particularly CIS by reducing the induced oxidative stress (caused by the medicines). SA searches for free radicals in the brain and has an effect as a hydroxyl radical scavenger. Anti - cancer properties of low dose aspirin is related to the inhibition of COX - 1 and thromboxane A2 (TXA2) synthesis by platelets. ASA used at low antiplatelet dose reduced primary cancer and metastasis incidence, but these effects are not certain in aged groups. Additionally, optimal dosage, duration of use, and ideal timings remain unknown to achieve anti - cancer effects in various types of malignancies, especially the ones which are non - gastrointestinal. ASA appears to have an impact on the lungs of patients with breast cancer. To elaborate, while long term treatment at a low dose doesn't significantly impact a number of metastases, it has a significantly negative impact on the phenotype of late - phase breast cancer. This is seen through several indications: decreased lung airiness, higher G - CSF concentrations in the lung homogenates, decreased local pulmonary and systemic NO bioavailability, increased GSSG/lower GSH concentrations in RBC, and some unfavorable changes in eicosanoid generation in the blood of mice. Moreover, breast cancer patients who received long term treatments exhibited increased infiltration of lung parenchyma by inflammatory cells along with increased serotonin concentration in the lung homogenate, suggesting a pro - inflammatory environment. To add on, it also resulted in increased production of G - CSF which increases neutrophil survival, potentiates their responses to chemotactic signals and increases immunosuppression. The administration of ASA or other NSAIDs enhances recruitment of hematopoietic stem cells. In plants, salicylic acid behaves as a phytohormone, controlling the various aspects of growth and development. It serves as an endogenous signal and using its antioxidant and antifungal features, it protects plants against pathogens [11].

Aspirin and flavonoid metabolites are effective in inhibiting cancer cell and tumour growth as large amounts are left unabsorbed in the intestinal lumen and therefore are subjected to degradation by the host and bacterial enzymes, "generating simpler phenolic acids". Both aspirin and flavonoids belong to the group of phytochemicals and are largely derived from naturally occurring plant sources. They both metabolise in the gut and the liver to produce several other metabolites [12].

Melanoma is one of the most fatal types of cancer due to its tendency to metastasize and resist therapy. However, SA and ASA are linked with promoting pro-apoptotic effect by activating ER stress and UPR with the help of PERK and ATF6 branches. Specifically, SA/ ASA have the ability to trigger ER stress, a physiological condition which is related to protein accumulation, protein misfolding, or other stress signals. So, in order to achieve intracellular protein homeostasis and survival, ER activates a number of reactions, such as an unfolded protein response. Furthermore, the 3 independent signaling pathways (PRKR - like ER kinase (PERK), activating transcription factor 6 (ATF6), and inositol requiring protein 1α (IRE1α)) which composes the UPR also promotes the expression of the transcription factor C/EBP homologous protein (CHOP), which signals cell growth arrest and apoptosis. Meanwhile, ASA and SA also cause the activation of AMPK, Akt and mTOR which are associated with cellular oxidative stress via activation of the nitric oxide generation enzyme eNOS. This increases nitric oxide and reactive oxygen species production inducing ER stress response. Both in vivo and in vitro experiments demonstrate that interference with ER stress in cancer cells, particularly melanoma, will significantly affect them psychologically and result in cell apoptosis. Additionally, SA and ASA also have a positive, indirect effect on cancer patients such as preventing myocardial infarct and reducing incidence of metastasis [13].

The fact that aspirin has the ability to rapidly deacetylate to form SA and previous in vivo and in vitro models have shown SA to be an antiproliferative and antitumor agent, partially explains SA's chemo preventive effect. While various studies account for the positive effect of SA on CRC, not taking into account many factors such as the complex relationship between genotype and metabolite levels and untargeted metabolomics approach will result in inaccurate results. Other limitations include the use of a weak instrument that doesn't proxy the metabolite levels and a small sample size. Overall, the study concludes that aspirin is insufficient at reducing CRC risk [14].

Aspirin consumption demonstrated a positive association in which at least 75 mg of dosage up to 5 years resulted in overall 20% decreased risk of dying from cancer. Aspirin consumption is related to a number of cancels including prostate (decreasing overall and advanced prostate cancer risk), esophageal and minimally breast cancer. There is, however, no clear association with melanoma due to inconsistent studies. Not only is aspirin associated with reducing CRC, it also decreases the risk for CRC relapsing post treatment. A wide spectrum of growth factors and pro - inflammatory cytokines triggers the overexpression of COX 2 at the sites of inflammation which then induces cellular transformation. On the contrary, aspirin reduces CRC specific mortality in those who suffered from the overexpression of COX 2. Also, high doses of NSAIDs can modulate the growth of cultured cells and bind and inhibit the 2 isoforms of COX.

Other potential anti - cancer effects of aspirin include reducing lung metastases in which "aspirin first affects platelets, then leads to a subsequent interaction between platelets and COX 2" [15].

Another research confirmed that aspirin metabolite salicylate induces programmed cell death in cancer cells. Aspirin has an effect on different types of cancer at various degrees as seen in multiple studies with little to no variation. For example, RCT's have shown the reduction of lung cancer mortality by 20%, risk of breast cancer by 25% and stomach cancer by 20 - 40%. However, it has little to no effect on pancreatic, ovarian, and prostate cancer. Apart from this, it can have a 90% survival rate in cancer patients suffering from acute coronary syndrome and thrombocytopenia. It can effectively be used along with chemotherapy because it reduces its side effects later [16]. A review clearly pointed out effects of Aspirin not only on cancer but how it holistically effects other diseases too. Although aspirin is administered to subjects in suffering from various diseases including Lynch syndrome, high risk of cardiovascular disease and inflammation, it also has some disadvantages such as increasing the risk of GI bleeding (but this is also dependent on patient's age, gender and ulcer history) and hemorrhage in patients older than 70. Like other NSAIDs, aspirin works by inhibiting cyclooxygenases - COX 1 is vital for the "production of thromboxane (TX), TXA2, which is involved in platelet aggregation and vasoconstriction" while COX 2 is expressed in inflammatory and hypoxic conditions. Aspirin has the ability to reduce the risk of CRC by over 25%. In non - malignant cells, nutrient - sourced carbons are mainly used to produce ATP while malignant cells "increase the import of nutrients from the tumor microenvironment and reprogramme CRC metabolic pathways, primarily to fuel biosynthetic processes". The reprogramming supports tumor development and "the switch to an increased glycolytic rate has been shown to occur early in CRC progression". Thus, a common therapeutic approach involves targeting cancer metabolism. Aspirin has various effects: it inhibits the phosphorylation and therefore activation of PI3K and Akt; mimic the effects of glutamine depletion on the cell cycle and biosynthetic pathways, by both inducing G1 arrest and causing mTOR complex 1 (mTORC1) inhibition; upregulates upregulate glutaminolysis - associated genes, large neutral amino acid transporter 1 (LAT1), and glutamic - pyruvic transaminase 2 (GPT2) in PIK3CA mutant CRC cells. It also downregulates many glutaminolysis enzymes resulting in decreased levels of glutaminolysis. Regulation of metabolic processes such as energy, nucleotide, and amino acid metabolism is key to the chemopreventive effect of aspirin as presented by the decreased risk of adenoma in human colon tissues of those who received 81 mg of aspirin. Aspirin can also acetylate several metabolic proteins and enzymes such as 14 lysine residues, glucose - 6 - phosphate dehydrogenase (G6PD) protein, pyruvate kinase M2 (PKM2) and lactate dehydrogenase (LDH) through a transacetylation reaction. Furthermore, acetylation of G6DP is vital as it is overexpressed in CRC patient and predicts poor prognosis. Moreover, aspirin targets the oncogenic pathways that are otherwise dysregulated in CRC where they also drive metabolic reprogramming in tumors [17].

2. Mechanism of Action

Many groups have predicted detailed mechanisms, either one of which could be involved in the anti - carcinogenic properties of Salicylic acid. The first one is the HIF pathway. Hypoxia is a common feature of solid tumors where the cells must rewire cellular metabolism - with the help of the transcription factor HIF - 1α - to favor glycolysis and therefore promote the Warburg effect leading to a downregulation of GLUT1, decreased glucose import, and reduced cellular proliferation HIF - 1α is commonly overexpressed in CRC and has been found to be associated with poorer prognosis. However, aspirin can decrease HIF - 1α resulting in a downregulation of GLUT1, decreased glucose import by inhibiting glycolysis and reduced cellular proliferation [18]. Another pathway is the NF - κB pathway which is a family of transcription factors which can induce the expression of genes involved in cell survival and inflammation. Elevated NF - κB activity in CRC cells plays a role in cell proliferation and survival. Moreover, it promotes glycolysis through the regulation of HK2 or GLUT3 and mediates metabolic reprogramming. While NF - κB drives a metabolic programme favoring glycolysis via the upregulation of GLUT1, aspirin downregulates GLUT1, resulting in decreased glucose import and lactate generation, antagonizing the Warburg effect [19]. Furthermore, the mTOR and AMPK pathway in which the mTOR, which exists as multiple subtypes, is a kinase complex involved in cellular survival and proliferation. AMPK is a critical energy sensor that monitors the ratio of AMP: ATP. Aspirin administration reduced mTOR signaling by inhibiting phosphorylation, and thus activating the downstream effectors and eukaryotic initiation factor which are important for protein synthesis. It alters the AMP: ATP ratio which causes AMPK activation to

restore it and finally causes the inhibition of mTORC1 [20]. Finally, the Wnt pathway involving Wnt signaling which plays an etiological role and influences metabolic reprogramming by favoring aerobic glycolysis. It also regulates the expression of PMK2 and LDHA which are involved in the promotion of the Warburg effect. Wnt5B can also suppress mitochondrial function by the c - myc signaling axis. Aspirin treatment can decrease the nuclear pool of β - catenin in CRC lines by the phosphorylation and inhibition of a specific protein that is a positive regulator of β - catenin. Also, "aspirin reverses the Wnt - mediated cystic phenotype in intestinal organoids by decreasing Wnt signaling and stemness marker expression". It can also decrease glutamine transporter expression and glutamine metabolism. Overall, aspirin targets this frequently dysregulated pathway in CRC and its metabolic consequences [21].

Another group of researchers showed that the mechanism involved is that aspirin affects the pathogenic pathways of neoplastic processes at a cellular level and the dynamic metastatic cancer spread. It disrupts the COX enzyme which is responsible for the formation of proteinoids that are key signaling lipids. They directly interfere with energy metabolism by targeting key enzymes involved in the proliferation of cancer cells as well as do this indirectly by inhibiting COX. Aspiring also interferes with the proliferative pathways, platelet - driven pro - carcinogenic activity and cancer - associated inflammation to inhibit cancer progression.

It also directly impacts angiogenesis, a process which allows cancer cells to grow and spread, in which it inhibits the overexpressed COX and directly modulates vascular - endothelial growth factor (VEGF) activity. It also stimulates the pro - apoptotic pathways and enhances the p53 mediated DNA repair. It can reduce metastatic cancer spread in which the platelets have a major contribution through a number of mechanisms including growth factor secretion, association of platelet aggregation with tumor cells, secretion of microDNA inhibitors of tumor suppressor genes and interfering with phospholipid metabolism resulting in pro - metastatic signals. Cancer patients also appear to suffer from increased vascular and thromboembolic disease events. Aspirin can reduce thromboembolism by blocking COX and inhibiting thromboxane A2 formation. The Mendelian randomization stands on the grounds that genetic variants avoid confounding and yield evidence similar to that of randomized trials. The biological effects of aspirin can be mimicked where the polymorphism changes the nucleotide in COX - 2, therefore reducing colorectal adenomas in polymorphism patients and colorectal cancer. Aspirin is also administered to patients suffering from Lynch syndrome, a dominant gene error associated with high risk of CRC and other cancer types, because it enhances the DNA repair mechanism. It is considered to be potentially prophylactic in which it has the ability to reduce the expression of MCM6 and RRM2 proteins (they are both involved in DNA repair) in human colon cells that is associated with increased colon risk cancer [22]. Another group further reconfirmed about the COX independent and COX dependent pathways. In the COX dependent reaction, aspirin suppresses the COX - 2 expression at multiple levels, an enzyme which is overexpressed in cancer. This results in a decreased production of pro - inflammatory prostaglandins such as PGE2, which are associated with cancer cell survival, migration, and angiogenesis. COX - 2 acetylation generates lipoxins which inhibit cell proliferation and angiogenesis. In the COX independent reaction, aspirin and salicylates inhibit IkB kinase (IKK) b and prevent NF - kB activation both in vivo and in vitro. NF - kB promotes transcription of many proteins that are involved in inflammatory responses and angiogenesis. Furthermore, the induction of human colorectal cancer also requires the activation of the NF - kB signaling pathway. It also interferes "with extracellular - signal - regulated kinase (ERK) signaling leading to its inhibition by preventing the binding of c - Raf with Ras". This ERK pathway is involved in cellular processes like proliferation, differentiation and survival. Other mechanisms under COX independent reaction include the inhibition of mitochondrial calcium uptake by salicylic acid resulting in anti - proliferative effects and the Wnt/b - catenin pathway. They further suggested that aspirin is mainly absorbed and then hydrolysed in the GI tract, but the hydrolysis can also take place in the liver and other organs. The acetyl group present in aspirin can acetylate several proteins apart from COX such as haemoglobin, DNA, RNA, histones, transglutaminase, hormones and enzymes. The acetyl group can reach large distant organs as it can bind to several proteins, glycoproteins and lipids of the stomach, kidney, liver and bone marrow. Additionally, it can acetylate the p53 protein or its mutants which are responsible for suppressing tumour. Aspirin is more effective in treating CRC as the intestinal epithelial cells are exposed to higher aspirin concentrations compared to other types of cancer which receive aspirin via the plasma which has lower concentrations of aspirin. The hydrolysis of large amounts of aspirin quenches it, resulting in high concentrations of salicylic acid exposed to the cells to interact cellularly and disrupt their activity with respect to NF - xB. Moreover, introducing electrophiles into the cells has the ability to alter their activity as they quench lysine and cysteine reactivity. These reactions are enhanced by "binding into the active sites to lower the transition state and then reacting to quench activity". Aspirin, therefore, similarly behaves when binding the COX enzyme. Low dose aspirin is considered to be equally effective as higher doses. The platelet hypothesis states that low dose aspirin's sequential inhibition to COX in platelets prevents platelet activation and the release of cytokines/growth factors/ lipid mediators at GI lesions sites. Other theories such as the inhibition of mTOR signalling leading to the activation of AMP - kinase, inhibition of Wnt signalling, inhibition of NF - κB, inhibition of polyamine synthesis and modulation of EGFR expression. after absorption, the aspirin is partially hydrolyzed to salicylic acid by esterases in the blood and liver which is then excreted or metabolised for elimination through kidney or bile. Aspirin can be metabolised in multiple ways: conjugation with glycine to form salicylic acid; conjugation with glucuronic acid; CYP450 enzymes in the liver; and in the gut by resident microflora. Additionally, aspirin's bioavailability can increase if it is administered with ampicillin. Aspirin metabolites have the ability to inhibit the CDK enzyme activity, cancer cell growth, and some metabolites can also inhibit cell proliferation in HCT - 116 and HT - 29 cells, demonstrating its role in preventing CRC. COX independent mechanisms also play a role in this. Additionally, HBAs are

selective in their modes of action as not all HBAs can successfully inhibit cancer cell growth [23]

3. Methodology

A survey was done to understand the awareness pattern for salicylic acid in individuals and how they understand the effects of the drug in reference to cancer and other dreaded disorders affecting our society. During the survey questions such as "According to your knowledge which products contain Salicylic acid" and "Do you think Salicylic acid has anticancer properties"

4. Results

Our survey showed that many people have been using salicylic acid around the world because of its cosmetic properties. The Fig 1.1 clearly shows that about 54.5 % of the individuals knew about Salicylic acid.

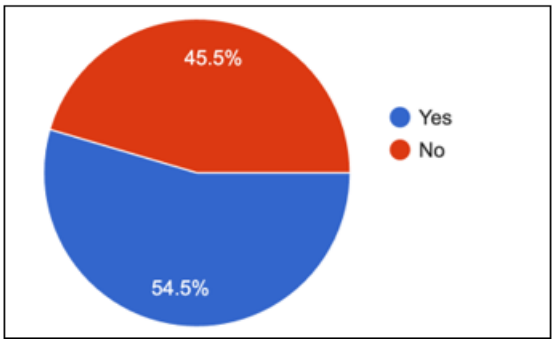

Figure 1: The Pie chart shows the result to the question "Have you ever used salicylic acid or its derivatives" showing that the it is a known chemical

Our study further showed that even though the name of Salicylic acid is not that known, but the derivative aspiring is widely used among the many other forms available in the market.

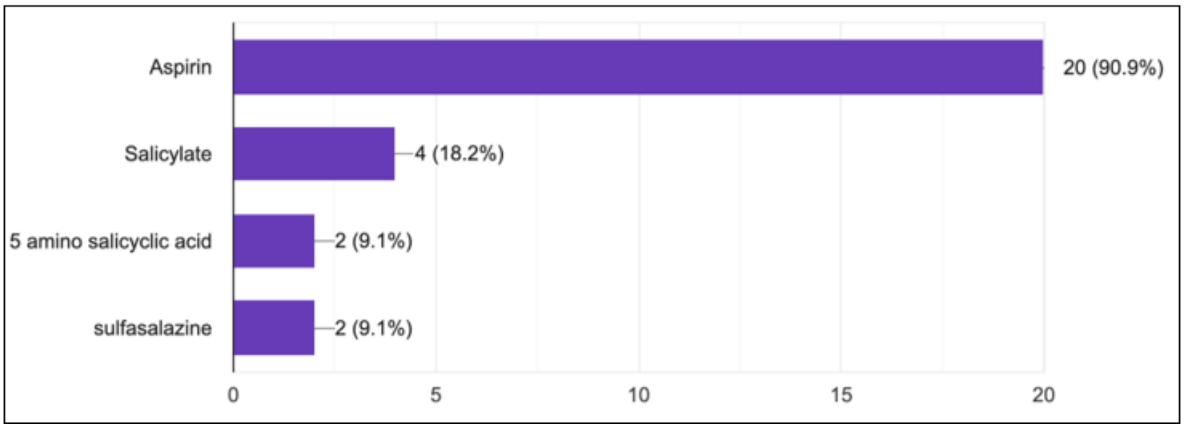

Figure 2: The graph clearly shows that Aspiring a well known name among individuals as compared to Salicylic acid or its other derivatives. It is known to about 90 percent of the people

Even though aspiring was a known name among the participants, most still believed that skin care products and medicines for fever have the derivatives of Salicylic acid. This is clearly shown in Fig 3. Also, people are still unaware of the anticarcinogenic properties of salicylic acid and its derivatives as shown in Fig 4.

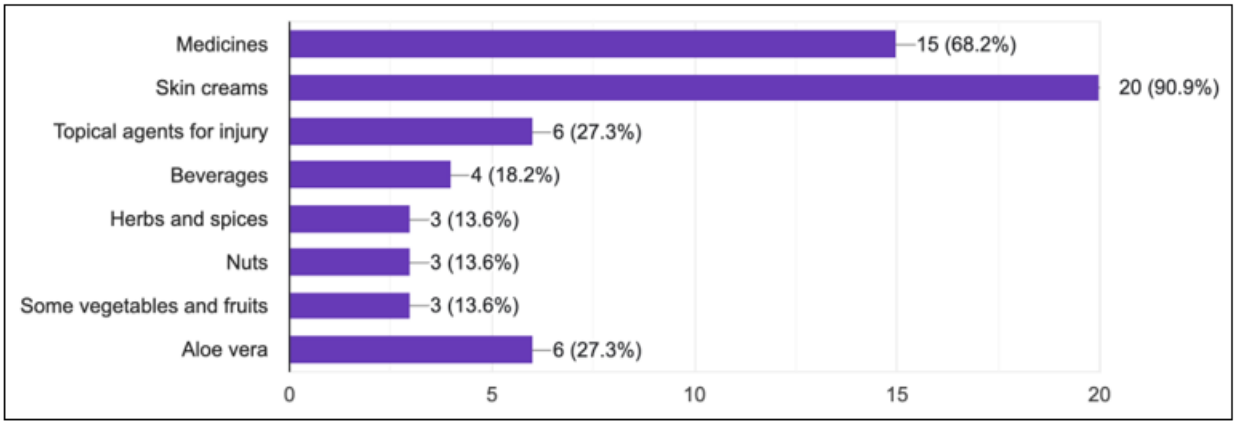

Figure 3: Shows the view of people on the presence of salicylic acid in various products available in the market

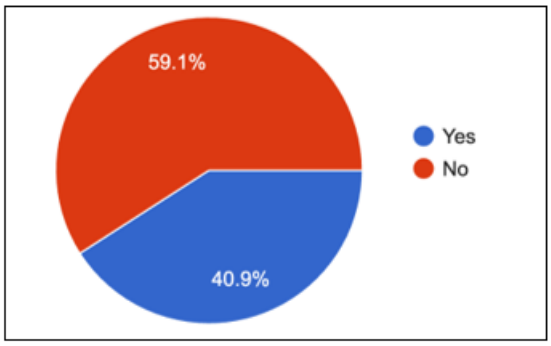

Figure 4: Shows that people still believe that it possesses no anticancer properties and is more of a cosmetic or a medicinal drug.

5. Conclusion

Understudied potential targets for aspirin: Aspirin's reactivity can be increased with structural interactions that increases the binding affinity "for either steric blocking of enzymatic transformations, or the covalent acetylation of nucleophilic functional groups to render proteins enzymatically dead". The 2 understudied targets are RNA and metabolites.

Conclusion- Acetyl and salicylate groups of aspirin have distinct targets but they both contribute to its anti - cancer effects. Acetylation is a unique characteristic of aspirin which is not present in other NSAIDs; it's a critical endogenous post translational modification that affects a range of proteins; has a ubiquitous nature; and can potentially control enzyme activity by activating, inactivating or destabilising metabolic enzymes. Cancer, for example, is one of the diseases linked with the deregulation of acetylation which is why identifying acetylated targets of aspirin and modifying their function can result in its chemoprotective properties.

Flavonoids and cancer prevention: based upon their chemical structure, flavonoids are divided into 6 categories which are extremely sensitive to the environment and can rapidly degrade under high temperature and unstable pH. They inhibit cancer through multiple mechanisms such as antioxidant properties or regulation of apoptosis, but they also downregulate Akt/mTOR pathway, induce mitochondrial mediated apoptosis, inhibit NF - κB pathway, attenuate Wnt signalling, activate AMPK and suppress abnormal epithelial cell proliferations just like aspirin.

Generation of HBAs through aspirin and flavonoid metabolism:

HBAs of Aspirin Exhibit Anti - Proliferative Effects in Cancer Cells: Dietary sources of HBAs - consumption of spices rich in salicylic acid; 2, 3 - DHBA present in fruits and vegetables, medicinal herbs, fermented soy products; 2, 5 - DHBA in plants and vegetables.

Metabolite hypothesis - The rapid hydrolysis of aspirin in the gut, the unstable nature of flavonoids, and the reports on the cancer - preventive potential of their degraded products through inhibition of cancer cell growth all point to the possibility that the HBAs produced from flavonoids and aspirin play a major role in their anti - cancer properties. Both, parent compounds and HBAs, play a chemo preventive role. The gut microbial enzymes may use unabsorbed flavonoids and aspirin/salicylic acid as substrates to transform them into simpler, pharmacologically active HBA from aspirin and flavonoids. The "metabolite hypothesis" shows how aspirin, flavonoids, and diet come together to form HBAs through the action of microbial and host enzymes.

→ effective cancer prevention requires the collaboration of parent compounds and the right microbial species responsible for HBA generation.

Clinical effects

Aspirin can increase the estimated survival by 5 years in men and 4 years in women who are suffering from CRC.

Vascular mortality significantly increases in patients who suffer from CRC as the patient may suffer from various diseases such as venous thromboembolism, coronary artery disease, stroke and heart failure. However, cancer can reduce the risk of venous thromboembolism

Adverse effects of aspirin

Aspirin increases the risk of GI bleeds, but these are usually seen in the early stage of development of the pathology responsible for the bleed and can be successfully treated. It significantly also increases the risk of cerebral bleeding, but this can be mitigated by monitoring the blood pressure before administering this drug.

Further research is required behind "dosage, duration of use and timing for initiation of the therapy" in order to achieve the best possible anticancer effects.

References

[1] Nounu, Aayah, et al. "Salicylic Acid and Risk of Colorectal Cancer: A Two - Sample Mendelian Randomization Study. " *Nutrients*, vol.13, no.11, Nov.2021, p.4164, https: //doi. org/10.3390/nu13114164. Accessed 1 Dec.2022.

[2] Arif, Tasleem. "Salicylic Acid as a Peeling Agent: A Comprehensive Review. " *Clinical, Cosmetic and Investigational Dermatology*, vol.8, no.2015, Aug.2015, pp.455–61, https: //doi. org/10.2147/ccid. s84765.

[3] Lin, Andrew N., and Thomas Nakatsui MD. "Salicylic Acid Revisited. " *International Journal of Dermatology*, vol.37, no.5, Wiley, May 1998, pp.335–42, https: //doi. org/10.1046/j.1365 - 4362.1998.00452. x.

[4] Dachineni, Rakesh, et al. "Salicylic Acid Metabolites and Derivatives Inhibit CDK Activity: Novel Insights into Aspirin's Chemopreventive Effects against Colorectal Cancer. " *International Journal of Oncology*, vol.51, no.6, Oct.2017, pp.1661–73, https: //doi. org/10.3892/ijo.2017.4167. Accessed 11 Dec.2020.

[5] Kulikova, Olga I., et al. "A New Derivative of Acetylsalicylic Acid and Carnosine: Synthesis, Physical and Chemical Properties, Biological Activity. " *DARU Journal of Pharmaceutical Sciences*, vol.28, no.1, Jan.2020, pp.119–30, https: //doi. org/10.1007/s40199 - 019 - 00323 - x.

[6] Kim, Jihye, et al. "Structure–Activity Relationship of Salicylic Acid Derivatives on Inhibition of TNF - α Dependent NFκB Activity: Implication on Anti - Inflammatory Effect of N - (5 - Chlorosalicyloyl) Phenethylamine against Experimental Colitis. " *European Journal of Medicinal Chemistry*, vol.48, Elsevier BV, Feb.2012, pp.36–44, https: //doi. org/10.1016/j. ejmech.2011.11.030. Accessed 2 Oct.2024.

[7] Florensa, Dídac, et al. "Low - Dose Acetylsalicylic Acid for Cancer Prevention Considering Risk Factors: A Retrospective Cohort Study. " *Annals of Epidemiology*, vol.84, Elsevier BV, Aug.2023, pp.60–66, https: //doi. org/10.1016/j. annepidem.2023.06.002.

[8] Kopp, Elizabeth, and Sankar Ghosh. "Inhibition of NF - KB by Sodium Salicylate and Aspirin. " *Science*, vol.265, no.5174, American Association for the Advancement of Science, Aug.1994, pp.956–59, https: //doi. org/10.1126/science.8052854.

[9] Smeda Id, Marta, et al. *Unexpected Effects of Long - Term Treatment with Acetylsalicylic Acid on Late Phase of Pulmonary Metastasis in Murine Model of Orthotopic Breast Cancer*.2020, www.ncbi. nlm. nih. gov/pmc/articles/PMC7135281/pdf/pone.0230520. pdf.

[10] Paterson, J. R. "Salicylic Acid: A Link between Aspirin, Diet and the Prevention of Colorectal Cancer. " *QJM*, vol.94, no.8, Oxford University Press (OUP), Aug.2001, pp.445–48, https: //doi. org/10.1093/qjmed/94.8.445.

[11] Cetin, Damla, et al. "The in Vitro Protective Effect of Salicylic Acid against Paclitaxel and Cisplatin - Induced Neurotoxicity. " *Cytotechnology*, vol.68, no.4, July 2015, pp.1361–67, https: //doi. org/10.1007/s10616 - 015 - 9896 - 3. Accessed 8 Mar.2021.

[12] Ausina, Priscila, et al. "Acetylsalicylic Acid and Salicylic Acid Present Anticancer Properties against Melanoma by Promoting Nitric Oxide - Dependent Endoplasmic Reticulum Stress and Apoptosis. " *Scientific Reports*, vol.10, no.1, Nov.2020, https: //doi. org/10.1038/s41598 - 020 - 76824 - 6. Accessed 11 Dec.2020.

[13] Nounu, Aayah, et al. "Salicylic Acid and Risk of Colorectal Cancer: A Two - Sample Mendelian Randomization Study. " *Nutrients*, vol.13, no.11, Nov.2021, p.4164, https: //doi. org/10.3390/nu13114164.

[14] Pasche, Boris, et al. "Prevention and Treatment of Cancer with Aspirin: Where Do We Stand?" *Seminars in Oncology*, vol.41, no.3, June 2014, pp.397–401, https: //doi. org/10.1053/j. seminoncol.2014.04.012. Accessed 12 Apr.2019.

[15] *Organised by the Aspirin Foundation Www.aspirin - Foundation. com - Sponsored by Bayer Schering Pharma AG*.2011, https: //doi. org/10.3332/ecancer.2011.213.

[16] Hoskin, Ashley J., et al. "Aspirin and the Metabolic Hallmark of Cancer: Novel Therapeutic Opportunities for Colorectal Cancer. " *Exploration of Targeted Anti - Tumor Therapy*, Aug.2023, pp.600–15, https: //doi. org/10.37349/etat.2023.00155. Accessed 21 Nov.2023.

[17] Stegen, Steve, et al. "HIF - 1α Promotes Glutamine - Mediated Redox Homeostasis and Glycogen - Dependent Bioenergetics to Support Postimplantation Bone Cell Survival. " *Cell Metabolism*, vol.23, no.2, Cell Press, Feb.2016, pp.265–79, https: //doi. org/10.1016/j. cmet.2016.01.002.

[18] Chen, Jingyu, and Lesley Stark. "Aspirin Prevention of Colorectal Cancer: Focus on NF - KB Signalling and the Nucleolus. " *Biomedicines*, vol.5, no.3, MDPI AG, July 2017, p.43, https: //doi. org/10.3390/biomedicines5030043. Accessed 6 Oct.2024.

[19] Henry WS, Laszewski T, Tsang T, Beca F, Beck AH, McAllister SS, et al. Aspirin suppresses growth in PI3K - mutant breast cancer by activating AMPK and inhibiting mTORC1 signaling. Cancer Res.2017; 77: 790–801.

[20] Gala, Manish K., and Andrew T. Chan. "Molecular Pathways: Aspirin and Wnt Signaling—a Molecularly Targeted Approach to Cancer Prevention and Treatment. " *Clinical Cancer Research*, vol.21, no.7, American Association for Cancer Research, Dec.2014, pp.1543–48, https: //doi. org/10.1158/1078 - 0432. ccr - 14 - 0877

[21] Elwood, Peter, et al. "Aspirin and Cancer: Biological Mechanisms and Clinical Outcomes. " *Open Biology*, vol.12, no.9, Sept.2022, https: //doi. org/10.1098/rsob.220124. Accessed 19 Sept.2022.

[22] Alfonso, L., et al. "Molecular Targets of Aspirin and Cancer Prevention. " *British Journal of Cancer*, vol.111, no.1, Springer Nature, May 2014, pp.61–67, https: //doi. org/10.1038/bjc.2014.271.