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Review Article

Current Advances and Applications in Animals, Plants and Biological Sciences

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Abstract

Plants' reliance on molecular epigenetic control reflects their developmental, lifestyles, and the evolutionary histories. Plants grows by continually developing new parts from the self-sufficing stem cells population, termed as meristem, as opposed to mammals, whose tissues and organs formation is primarily determined during the embryo development. The interest in different medically active products has been developed to improve their pharmacokinetic and biological properties for utilizing glycosyl-conjugation. The conjugation of various drugs with various mono, di, or polysaccharides has boosted the therapeutic potentials of these drugs that is also manifested by a significant number of research papers. The current review article encapsulates extremely important and the up-to-date example of this conjugation, specially associated to enhancing antitumor activities of original glycoconjugates. The given examples along projected mechanisms of activities enhancement may guide to design, synthesize and evaluate new glycosyl conjugates for improved therapeutics.

Keywords: Antibacterial, Glycosylation, Antitumor, Antioxidant, glycosyl conjugates.

INTRODUCTION

As a result, post-embryonic developments in the plants are continual procedures influenced by environmental factors, leading to a higher degree of phenotypic flexibility. Because plants cannot avoid their surrounds, they are compelled to adapt to changing and frequently un-favorable environment condition [1-3]. Molecular epigenetics regulatory techniques can help plants to reproduce and survive in unexpected conditions by facilitating stable variations in the gene activity and fitting gene-expression pattern. Molecular polyploidization, or the growth in numbers of chromosomes sets, is ubiquitous in plants, expanding families of genes and promoting the functional capacity of duplicated genes, as well as those participating in the control of molecular epigenetics [4, 5]. Understanding plant epigenetic regulatory mechanism has mostly come from the genetic screens, particularly in *Arabidopsis thaliana*, a part of mustard family which is very susceptible to the genetic analysis and it was the 1st species of plant to have sequenced genome. The crop plants, especially *Zea maize*, have also made significant contributions to understand the epigenetic institutional arrangements and epigenetic phenomena. Plant epigenomics and molecular epigenetics have long historic evidence and together with analogous investigations in fungal and animal systems, they are considerably contributing to our fundamental understanding of epigenetic control [6, 7]. Numerous fundamental advancements to the subject of molecular epigenetics have come from the plant studies. Among these the differentiation between the heterochromatin and euchromatin are based on the cytological analysis. The discovery in maize and tomato of heritable alterations in gene expression state upon interaction to an allele with an alternate state, termed as para-mutation, was initial indication for inheritance of non-Mendelian epigenetic, which is now seen in plants, flies and mammals. Parental embedding of specific genes, which is single allelic expression

from either paternal or maternal origin, is mechanism its dysregulation is at the root of variety of genetic illnesses in humans [8, 9].

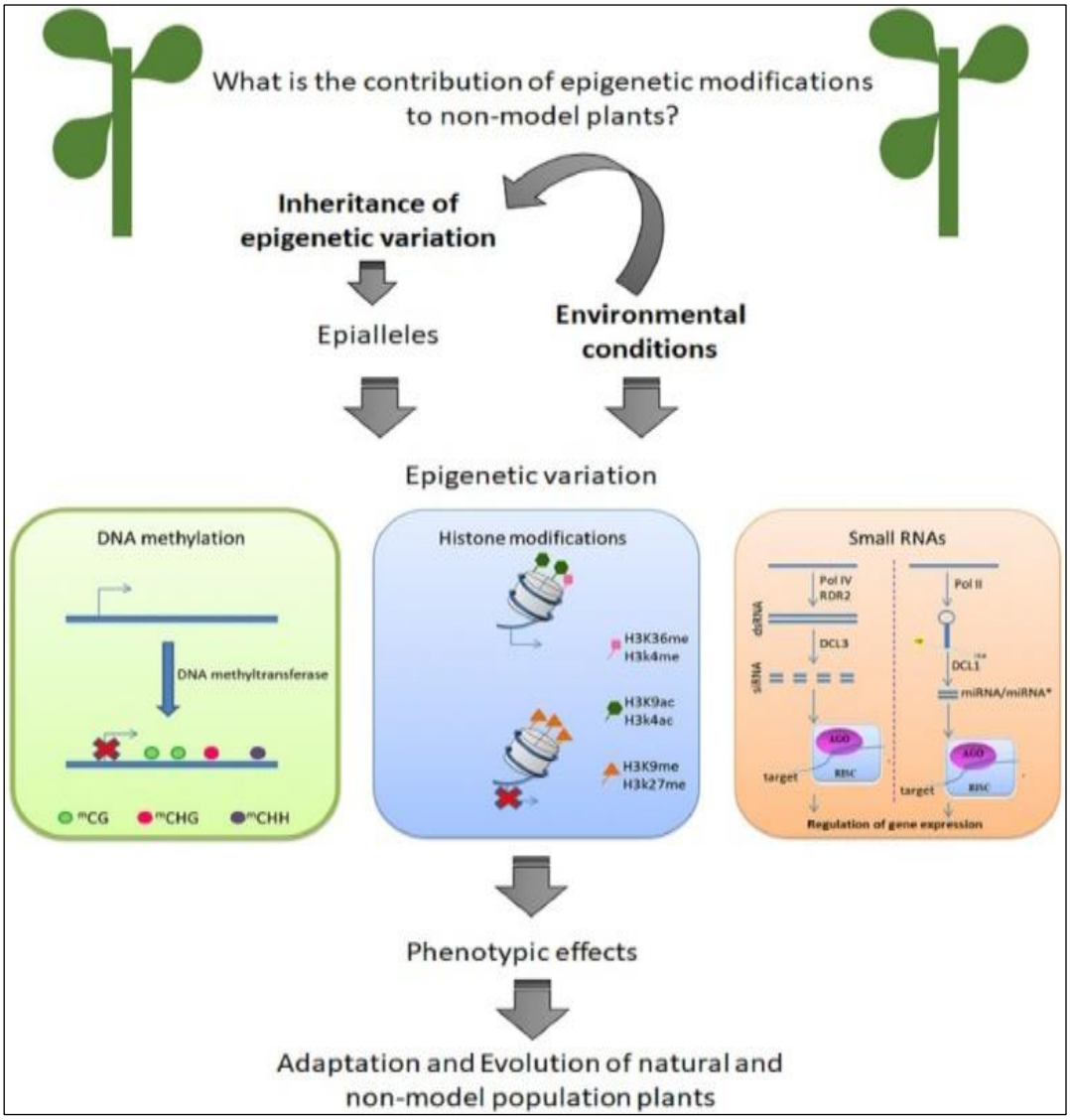

Figure 1: Shows the Molecular epigenetics regulation in plants

Glycoconjugates are basically saccharides (carbohydrates) covalently bonded with its non-sugar partner specifically lipid or protein. These conjugates are mostly found outside the cell membrane and are involved in events such as specific recognition event occurring among the neighboring cells. Oligosaccharides are branched in their stricture often constituting the three major bio-polymers together with nucleic acids whereas the nucleic acid and protein are linear. The hydroxyl group present on each monosaccharide allows the other monosaccharides to bind with it through glycosidic linkage that can have different stereoisomers in α and β configurations. Glycosylation is very important enzymatic process in biology by which the glycones are linked with biological molecule like proteins and lipids. The process of central dogma (transcription and translation) is important in glycosylation of these products. Evidences have been evolved which show that the post-translational process is significant in glycosylation of proteins in mitochondria, Golgi apparatus and plasma membrane. This glycosylation plays vital role in stability of proteins, cellular interactions, cell adhesion, signal transduction and in protein folding even. Therefore, a minor fault in the glycosylation may lead to serious metabolic, neoplastic and neurodegenerative disorders [1-6]. The classification of these glycosidic linkages is done on the basis of functional group on amino acids of protein part conjugated with the sugars. About 37 glycosidic linkages have been yet identified in living organisms, based on eight amino acids and thirteen monosaccharides. The renowned classes among them consist of S-linked, N-linked, O-linked, C-linked, and P-linked glycoproteins. Amid them, N- and O-linked glycoproteins are most common [8-10].

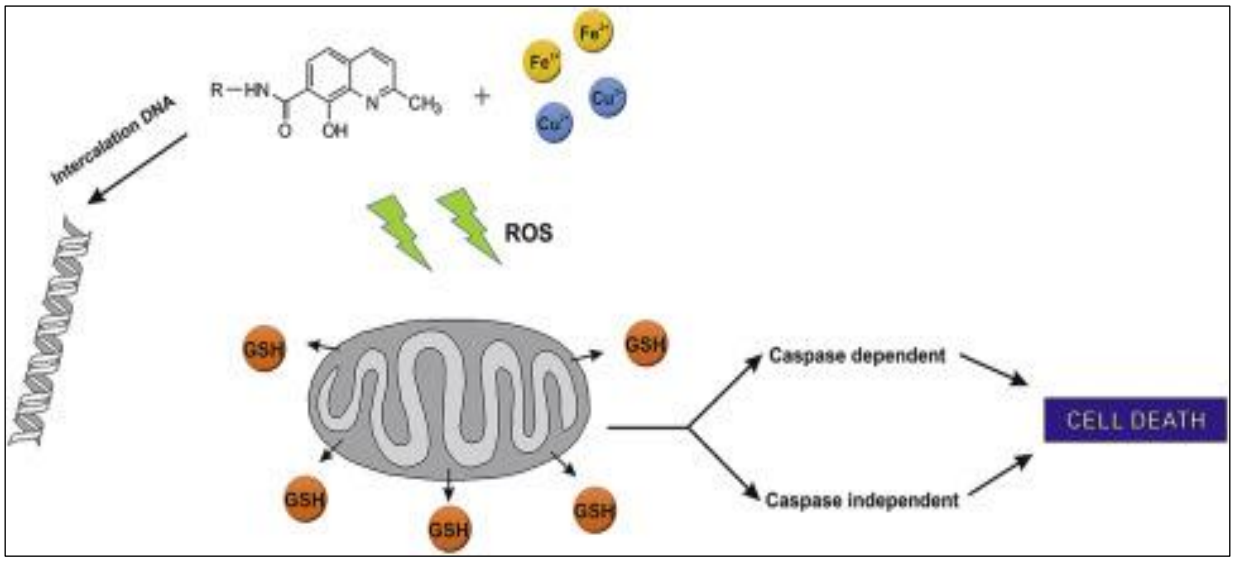

Figure 2: Derived glycoconjugates and their antitumor studies

The consumption of higher glucose level by cancerous cells was used as an indicator of cancerous tissues presence and it is also used for the patience response assessment for the treatment of cancerous tissues. If the radio-label glucose analogue named as 18F-FDG in the cancerous tissues is identified then these markers/indicators of cancerous tissues can be verified using the process of positron emission tomography [10]. Including brain and bladder, the tissues with highest ability to consume sugars for adopting these analogues for the healthy individual. However, for the patient suffering from cancer the high glucose consuming tissues are not concentrated, rather the selective cancer cells are observed. This is certainly accredited to the dominant expressions of GLUT-1 [11-13]. The future perspective of carbohydrate science can be associated with the application of its products; thus, the applications and synthesis of glycosidic conjugates is necessity of the time. Hence these perspectives are the backdrops of this review in which synthesis of these conjugate molecules rightly observed.

Glycosylation is known as the novel trend for the anti-tumor activities improvement

In the early 1990s, the awareness has been established to graft mono-, di- or poly-saccharides to several cytotoxic-agents using N, S, and C or O-glycosidic-linkage. The resulting conjugates exhibited enhanced solubility of water, improved aglycones targeting and stability of serum to the cancer tissues [14-18].

O-glycosylation for the enhancement of aglycone-cytotoxic-activity

Glufosfamide is a glycosylated ifosfamide and it was observed to rise the reduction and selectivity in toxicity of the original cytotoxic-drugs. The consequences exhibited an enhancement in the test animals' survival time, who obtained glufosfamide with LD-50 by the 4.5 times greater for rats and 2.3 times for the mice as compared to those having ifosfamide [19]. The critical trials were carried out on human beings with tumors of different origins regarding glycosamide on twenty patients. The maximum tolerable dose to be determined was 190 mg/kg, that is more less than that of ifosfamide (530 mg/kg); subsequently, the deadly side effects of glufosfamide were reduced when compared to the free-aglycone. Results showed that the ten patients kept living with the constant disease, two experienced a positive retort with having one of them completely remitted for greater than 4 years whereas the residual 8 patients suffered advance of their disease [20]. It is connected paclitaxel at the position seven and ten worked improving the cytotoxic action and minimize the toxic side effects of toxoids with many mono-saccharides including galactose, xylose, glucose and mannose. The consequences presented that the four conjugated glycosyls being linked at 10^{th} position had more water solubility with improved cytotoxic activities compared to non-glycosylated molecules [21]. At paclitaxel positioned on 4 are newly synthesized novel glycosyls conjugated through Ester molecules and at 2^{nd} position are with Ether linkage [22]. Podophyllotoxin is a kind of natural aryltetralin from lignin family and it is extracted from *Podophyllum peltatum* roots. This product naturally possesses an effective cytotoxic activity against certain cancerous cell-lines acting at binding site of colchicine on the tubulin. The greater toxicity and the less solubility of water are major hindrances of podophyllotoxin application as an anti-cancerous drug. There have been numerous efforts done to control such problems like formation of per-butyrylated riazolyl podophyllotoxin glucosides.

The compound showed maximum cytotoxic activity against five different cancerous cell lines having IC50 with alternate ranges between 3.27 ± 0.21 to 11.37 ± 0.52 µM [23]. Many kinds of tumors like

lung, neck, colorectal, ovarian and head cancers are being cured using platinum (IV) prodrugs. These drugs are mostly activated by intracellular reductions followed by the cellular uptake. It is manufactured a glycosylated platinum (IV) series of pro-drugs, purposely to improve their stability as a chemical and tumor specificity according to Warburg phenomena. The corresponding results revealed that these compounds have a greater cytotoxic activity of about 166 times greater than oxaliplatin, satraplatin and cisplatin [24]. There are synthetic antitumor agents known as Glycosylatd Antitumor Ether Lipids (GAELs) which can inhibit the cytotoxic activity in cancerous stem-cells which is responsible for the tumor's degeneration. The 2-amino-2-deoxy-D-gluco-GLN is a GLN that exhibited enhanced anti-tumor activity versus cancerous cells of epithelium along with their stem cells. This action was conjectured to be because of the production of acidic-vacuoles releasing acid leading to cell death which could be reasoned due to the existence of amino group on sugar part. The hypothesis has been elaborated with the formation of bis-amino GAEL compounds that possess 2-3 times more effective activity on test cancerous cell -lines and also against their stem cell as compared to GLN [25]. Newly synthesized O-glucosylated coumarin-pyrazoline derivatives and their cytotoxic effects on the two human cancerous cell-lines were studies in-vitro and the two cell lines observed were esophageal cancerous cell-line (SKG) and breast cancer cell-line (MCF-7). The consequences revealed that O-glycosylated compounds have better anti-tumor activity against the test cancerous cell-lines as compared to their non-glycosylated -compounds. These consequences highlighted the significance of the glycosylation to enhance the site-selectivity of the original compounds [26-27].

N-glycosylation for the improvement of aglycone cytotoxic activities

There have been a huge number of efforts done to study the character of N-linked-glycosylation to check the cytotoxic activities of their conjugate aglycones [28-30]. It is manufactured a novel class of compounds known as five coordinate Pt(II) using either pyridine or imidazoline linker by conjugating N-linked sugar molecules. These compounds when compared with cisplatin showed better cytotoxic activity on cancer cell lines that being observed including MCF7 and epidermoid-carcinoma cell-lines (A431). The consequences showed that N-glycosylation, from X-ray crystallography, improved apoptotic activities with improved interface among DNA and protein. The compounds have the best antitumor activity against test cancer cells [28]. The compounds comprising 1,2,3-triazolyl-1,3,4-thiadiazole-Nglucoside have been newly synthesized and they were examined regarding their cytotoxic activity versus the two cancer cell lines i.e. (MCF7) and humans colorectal-carcinoma (HCT116) cell line. The consequences revealed that the compounds have greatest activities against test cancerous cell-lines. These consequences evaluated the importance of N-glycosylation to pay for a novel triazole scaffold to improve the cytotoxic activities of such heterocyclic compounds [29].

Another newly synthesized novel series of styryl pyrazole N-glucoside has been investigated about the cytotoxicity on human adenocarcinoma cell line (AGS). It was concluded that there is an improvement in cytotoxic activity more specifically for the compound and they have an IC50 of 73 µM compared to their non-glycosylated compounds with an IC50 greater than 100µM. This improvement can be indication of how N-glycosylation is important for improving the site selectivity on the basis of Warburg phenomena [30].

S and C-glycosylation for the improvement of aglycone

To enhance the cytotoxicity and reducing the hazardous side effects of existing anti-cancer agents, investigation on cytotoxicity of C-glycosylation as a new strategic approach can be helpful. Cucciolito et al used D-galactose and D-glucose to link them with either C-1 or C-6 of platinum complex. A compound 1gal1-I was observed to have effective cytotoxicity with an IC50 15.2 ± 0.3 µg/ml and 3.9 ± 0.3 µg/ml in murine BALB/c-3T3 cells and fibroblast SVT2 cells respectively using MTT assay for next to 48 hours of incubation as compared to other glycosylated platinum complexes. This betterment in cytotoxicity can be attributed to the enhanced complex stability of biological medium and increased selectivity of tumor cells that are dependant on Warburg effect [31]. Newly developed compounds like 8-C- -D-(3"-O-acetyl) glucopyranosyl apigenin extracted from *Ocimum basilicum* leaves. The compound was observed to be strongly cytotoxic agent versus cancerous cell-line of human colon (HCT-116) and was compared with the eighty percent crude form of ethanolic extracts of the plant. This enhanced anti-tumor activities showed its significance [32]. The effect of S-glycosylation compound on cytotoxicity of certain anti-tumor agents has been studied. In this case, it is investigated the cytotoxicity of thioglycoside derivatives of (1,3,4-thiadiazolyl) thiaazaspiro [4,5] decane and thiazopyrimidine against three cell lines, i.e., HepG-2 (human liver hepatocellular carcinoma), HCT-116 (human colorectal carcinoma) and PC-3 (human prostate adenocarcinoma). The results revealed that that how these enhanced cytotoxic activities on test cell lines as compared to their equivalent aglycones [33-36].

CONCLUSION

Glycosylation of effective pharmacological agents represent a novel field of research for enhancement of pharmacokinetic and biological properties of their aglycones. This review paper represents some of the very novel studies in this field of enhancing the anti-oxidant, anti-tumor and anti-

bacterial activities of such glycosylated products with their comparison to their pure aglycones by means of exploring the probable procedures of changes in their activities. The given results may provide a guideline to develop new products having better biological activity based on their conjugation with various sugars.

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