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The production of water-soluble derivatives of natural menthol for commercial applications: A comprehensive review

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Abstract

Menthol is also a significant essential oils (EOs) constituent extracted from different plants like palmarosa, lemongrass and eucalyptus. Now-a-days, menthol is extensively used in various pharmaceuticals, pesticides, oral hygiene products, cosmetics, confectionary and also as flavouring agent. Despite a lot of importance of menthol in various field, its slight water solubility and capability to sublimate after storage have limited, its wider use. Hence, in the present review modification of menthol into water soluble glycosides has been discussed comprehensively. As monoterpene glycoside compounds have attracted the attention of various researchers in recent years as storage-stable, odorless pro-aroma and water-soluble molecules that under controlled chemical reaction conditions may break down to the respective aroma substances. This controlled release of aroma by odorous compounds has fascinating potential applications in cosmetics and food industries. The slow yet controllable glucoside hydrolysis achieved by appropriate hydrolases, causing long lasting perception of flavour and aroma. Glycosylation method is generally used to the conversion of menthol into menthol glycosides. This method can improve phenolic compounds' biological activity by increasing their water solubility and improving their pharmacological properties, and it can even provide phenolic glucosides new biological functions.

Keywords: Menthol; Glycosides; Monoterpene; Water solubility; Glycosylation

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1. Introduction

Menthol is a naturally occurring compound and chemically known as 2-ispropyl-5methyl cyclohexanone. Menthol is also a significant essential oils (EOs) constituent extracted from different plants like palmarosa, lemongrass and eucalyptus. Now-a-days, menthol is extensively used in various pharmaceuticals, pesticides, oral hygiene products, cosmetics, confectionary and also as flavouring agent [1-2]. As far as its medical uses are concerned, both prescription and over-the-counter medicine containing menthol are now available for different diseases treatment such as gastrointestinal disorders, musculoskeletal pain respiratory diseases and common cold [3]. Furthermore, menthol is commonly employed as part of antiseptic, analgesic, cooling formulations and topical antipruritic. Around 30,000 metric tons of menthol are expected to be consumed annually [4]. In culinary industry, menthol is among the most important flavouring compounds after citrus and vanilla. It is also commonly added in various tobacco products [5]. Despite a lot of importance of menthol in various field, its slight water solubility and capability to sublimate after storage have limited, its wider use. However, isolation of I-menthyl-p-oglucopyranoside (monterpene glycoside) [6] from the mint plant revealed that this compound has good water solubility and also little capability to sublimate after storage. Hence, this discovery opens the door of the research for finding the appropriate methods for the synthesis of monoterpene glycosides.

The glycosylation of substances with phenolic or alcoholic groups is a useful technique used to improve the water solubility and stability of various compounds [7]. The glycosides synthesis is of interest in several industries like cosmetic, pharmaceutical, nutraceutical and food [8]. One of the main disadvantages in the carbohydrates-containing compounds study is the existence of pure compounds in natural sources in low quantity. Hence, chemical or enzymatic methods are thought to be provide significantly larger chirally pure compounds quantities. The essential requirement to synthesize alpha or beta glycosidic bonds with full stereoselectivity is the major reason why chemical process of O-glycosylation is considered to be one of the modern synthetic chemistry challenges. However, in nature, there is no question related to the glycosylation stereoselectivity, as these reactions are take place under the influence of enzymes which are selective and specific in nature [9].

2. Methods of glycosylation

Glycoside compounds can be chemically synthesized by various processes which are depend on the activation of leaving group present at anomeric center [10], these are may be chemical methods or enzymatic methods. Nevertheless, all chemical synthesis methods involving the conventional Koenigs–Knorr reaction cause poor selectivity, low yields, tedious purification processes, and necessity of protecting groups. The selection of chemical glycosylation or enzymatic glycosylation is based on various factors which are as follow [11]. (a) The harsh chemical reaction conditions required to decompose the unwanted anomers or labile aglycone are formed, (b) heavy metal catalysts use is not desirable due to their toxicity and high price (particularly for those products which are employed as pharmaceutical drugs or in nutrition and food and), (c) enzymatic glycosylation help to avoid sterical hindrance due to less bulky unprotected, glycosyl moieties are employed; (d) the enzymatic process can help to glycosylate the substrates of high water solubility, (e) expensive aglycones may be recovered in enzymatic process. Thus, enzymatic glycosylation of menthol is a valuable alternative technique because of the regio as well as stereoselectivity of the enzyme catalyst. Further, mildness of reaction conditions for the process, as compare to chemical methods made it potential technique to synthesize menthyl glycosides derivatives [12].

2.1. Chemical glycosylation

Chemists have been trying since the early days to solve the problems related to the glycosylation stereoselectivity. At the end of nineteen century, Michael performed the first reaction for aryl glycosides synthesis and Fischer performed reaction for alkyl glycosides synthesis and showed the glycosylation process complexity [13]. There are various types of the glycosylation depending on the bonding bridge between donor and acceptor compound. In the present research O-glycosides are of interest as "O" links the menthol molecule with glycoside molecule. *O*-glycosides are generally synthesized by the protection and activation of glycosyl donors having several leaving groups and phenols or alcohols as glycosyl acceptors [14]. Koenigs and Knorr are credited with discovering the first general, controlled glycosylation process for the synthesis of oligosaccharide. This method suggests the nucleophilic bromine or chlorine displacement at the anomeric centre. The glycosylation process was performed using Ag_2CO_3, (function as acid scavenger) [13]. Various glycosides of terpene were prepared by using Koenigs-Knorr method [15] in the presence of silver compounds like Ag_2O, Ag_2SiO_3 Ag_2CO_3, which act as promoters. Good glycosides yield of hindered alcohols was obtained using silver trifluoromethanesulfonate that needs ahindered base 2,6-di(*tert*-butyl)-4-methylpiridine (as scavenger of trifluormethanesulphuric acid). Schmidt and co-workers developed a trichloroacetimidate method, that is generally superior over the Koenigs-Knorr method, especially for the hindered glycosyl acceptors. At relatively mild acid catalysis, *O*-glycosyl trichloroacetimidates are used as strong glycosyl donors [14].

2.2. Enzymatic glycosylation

Due to the reaction mildness and selectivity of the enzyme, glycosylation in the presence of enzyme is a valuable process for the reactions of complex substances of biological importance as compare to chemical methods in which usually harsh chemical reactions conditions or the requirement of toxic catalytic substances are undesirable [16]. In food additive chemistry, tthese methods (involving enzyme catalysis) are considered as a suitable alternative where the synthetic chemistry use is often unacceptable. In biotransformation techniques, a variety of alternative tools of glycosylation may be applied. The use of glycosyltransferases (GTs) is one of them, which usually use sugars (activated by nucleotides) as glycosyl donor [17]. The strict specificity of certain GTs remains a limiting factor in glycosylation of natural products, but the natural-product GT promiscuity may be expanded through direct evolution by the use of GT engineering as well as evolution platforms [18]. Furthermore, the use of specific activated glycosides (aromatic in nature) in order to attain the equilibria of the reactions catalyzed by GTs has been analyzed [19], which shows an improvement in the process of glycodiversification for small molecules. The transglycosidases (TGs) are used for the synthesis of saccharides by the transfer of a glycosyl group from one chain of carbohydrate to other one [20]. It is also possible to use whole cell biotransformation systems, which are capable of cofactor regeneration, like plant-cell cultures, bacteria and fungi etc. The glycosyl group transfer between oxygen nucleophiles is catalyzed by glycoside hydrolases (GHs) (also known glycosidases). The β(1-4)-glycosidic bond hydrolysis between the terpene aglycone of glycosides and monosaccharide results from these types of transfer reaction. The glycosylation reactions catalyzed by glycosidases may be controlled thermodynamically (reversed hydrolysis, direct glycosylation) or kinetically (trans-glycosylation). In trans-glycosylation, high yield of the product can be obtained in a small time as compare to direct glycosylation. However, direct glycosylation is preferred if there is a possibility of getting high yield of the product [20]. Hence, catalysis of glycosylation reactions in the presence of enzymatic catalyst is a powerful method not only for the enantioselective and regioselective synthesis of various biologically active substances but also for the production of less toxic, active and new (like glycosides) for the biologically active natural products and also it yields significant metabolites quantities that are difficult to get either chemical or biological synthesis [21]. Environmental issues have emphasized on the cleaner methods development. Besides, reusability and recycling of catalytic materials are now being given a great deal of attention. That is why, biotransformation processes using biological systems to cause chemical changes in both natural as well as synthetic substances provide an enticing alternative method as compare to conventional chemical methods. Under moderate conditions, biotransformation occurs without producing radioactive waste [22].

3. Enzymes used for glycosylation

Chiral flavours frequently exist in nature in the form of single enantiomers. As different regioisomers or enantiomers could show several sensorial properties, it is beneficial to synthesize them separately [23]. Biocatalysis is a useful tool to catalyze a large number of regio and

stereoselective chemical reactions that are difficult to perform using classical synthetic processes. There are around 25,000 enzymes in nature and around 400 enzymes have been commercialized, primarily for stereoselective synthesis of organic compounds and also for the flavour compound synthesis by biotechnological process. Enzymes have a global market of more than $1 billion dollars. Moreover, the increasing ecological systems sensitivity supports the use of environmentally friendly procedures [24] and increasing demand for the natural flavours has resulted in significant scarcity of numerous plant resources like strawberry aroma Many oils and pure aroma chemical constituents extracted from plants are available for above 5000 dollars per kilogram. For example, 4-decalactone produced synthetically, a peach flavour compound costs 150 dollars per kilogram, whereas the same chemical extracted from natural plant costs 6,000 dollars per kilogram. The enzymes mostly used in for the synthesis of stereoselective compounds include transferases, hydrolytic enzymes, lyases and oxireductases. Microbial enzymes play an important in the synthesis of flavour compounds [25]. Monoterpene alcohols like menthol, citronellol, geraniol, and linalool have a significant role in both fragrance as well as flavour industry. In addition, these compounds have useful applications in agrochemistry and pharmacy [26]. Geraniol is estimated to constitute 43% of the fine fragrances present in market. Enhanced stability and good solubility in water of these volatile compounds would be attained by the glycosylation to non-volatile and non-odorous sugar conjugates. Though, terpene alcohols are released easily from their respective glycosidic precursors through enzymatic or acidic hydrolysis. This delayed and controlled release mechanism of the fragrance and aroma has a fascinating industrial potential. Various toxic catalysts, high pressure, temperature, water-free conditions, and several steps for functional groups activation, protection and deprotection are used in chemical glycosylation process. In order to avoid all above harsh reaction conditions, enzymatic glycosylation is preferred. Geranyl glucoside was thus formed by reversed hydrolysis of geraniol and glucose in the presence of β-glucosidase (derived from almond seeds) in two phase spray column reactor [27]. The product's adsorption on alumina was applied in-line successfully. Using an initial 50,000 enzyme units, about one kg of geranyl glucoside was synthesized in two days. Glycoside synthesis by the process of reverse hydrolysis, however, suffers from operating at high concentrations of the substrate and low acitivity in water, and from the attempt to remove and purify products from high educt amounts. There are still poor yields based on the costly aglycone. In addition, transglucosylation geraniol in the presence of *β*-glucosidase (extracted from *Trichoderma citrinoviride*) was analyzed when the donor of glucoside was *p*-nitrophenyl glucoside. But other alcohols like linalool, octanol and hexanol were not accepted [12]. Further enzymes were used in glycosylation process are summarized in table 1.

α-Glucosidase is a widely distributed enzyme found in animals, plants and microorganisms. It catalyzes the release of α-glucose molecule from the non-reducing α-glucosides ends like sucrose and maltooligosaccharides. Specificity of substrate is varied greatly, depending on the source of enzyme [28]. The transglycosylation activity of α-glucosidases is used in the industry to produce oligosaccharides and sugar conjugates as biologically useful materials, aiming to improve their chemical properties and physiological functions [29-30]. In the pharmaceutical and food industries, α-glucosidase enzyme plays an important roles in the synthesis of several oligosaccharides types like nigerooligosaccharides, isomaltooligosaccharides, and some glucoside compounds like menthyl α-D-glucoside [31], α-D-glucosylglycerol (αGG) [31] and α-D-glucosyl vitamin E. Glycosylation of non-sugar molecules is an important and useful method to improve their physicochemical (water solubility and stability) and biological properties [32]. Furthermore, α-glucosidase enzyme has already extensively been used to synthesize glycoside compounds at industrial level as this enzyme had long achievements in the synthesis of oligosaccharide and also available at low cost. The produced glucosides in the presence of α-glucosidase enzyme are, of course, far more valuable as compare original materials. α-amylase enzyme is present in wide variety of organisms and used for the metabolism of starch (source of energy and carbon). α-amylase enzyme is also included one of the most abundant enzymes used at industrial scale mainly for the synthesis of starch derivatives due to its high efficiency as well as low cost. It's surprising that the α-amylase enzyme could provide a high glycoside yield by using a cheap, big soluble starch molecule (with ∼100polymerization degree of) as the glycosyl donor [33]. Despite the extensive research on the properties and structure of α-amylase enzyme and the several reports in the literature on transferase reactions, little attention has been given to glycosylation using α-amylase. α-Amylase enzyme acts on the substrate via “retention mechanism” and also as “transferases” (catalyzing the oligosaccharides synthesis using sugars to accept the transferring oligosaccharides instead of water. Moreover, amylase enzymes have been categorized as “saccharifying” or “liquefying” based on their degree of depolymerization of starch molecules. Abundance of starch as substrate, α-amylase has enormous potential for glycosylation reactions. In previous research it has been observed that α-amylase extracted from *Aspergillus oryzae* successfully catalyzed the glycosylation process by transferring the maltose to butanol, ethanol and methanol This enzyme was also observed to transfer glucose molecules to polyols from the low polymerization degree oligosaccharides. In another study, α-amylase extracted from *Bacillus subtilis* X-23 was observed to have capability to transfer glucose molecules and even oligosaccharide compounds to hydroquinone when soluble starch, maltopentose and maltotriose were used as substrates [34].

4. Glycosyl derivatives of monoterpenes

GBVs (glycosidically bound volatiles) are a new class of secondary metabolites of plant, which are present in very low concentration. In addition, GBVs are colorless and non-volatile compounds, therefore are not analyzed directly by gas chromatographic (GC) and sensory analysis Though some phenomena like the increase in EO contents during peppermint storage suggested the existence of bound monoterpenes, the first GBVs (citronellyl glucoside, geranyl, neryl) were observed in rose petals [35]. The glucoconjugated monoterpenols discovery focused the attention of researchers on the GBVs study [36]. Since then, compounds of GBVs class have been successfully isolated from non-essential oil

and essential oil bearings plants and characterized structurally. GBV compounds have been analyzed in about >50 plant families, and it was also found that the GBVs are not only exist in aerial part of plants but also in rhizomes, roots, seeds and petals [37]. However, the GBVs presence in grape plant was already observed in 1974 [38], in food crop, monoterpenyl glycoside compounds were first analyzed in 1982 [39]. The early stage of GBV study was marked by the spectroscopic structural identification of GBV compounds purified by chromatography and the investigation of plant volatiles produced from glycosidic extracts upon acidic or enzymatic hydrolysis. Glycosyltransferase enzymes that are thought to form GBV compounds have been difficult to isolate and characterize, because of their low catalytic activity, low abundance and the lack of appropriate detection techniques for the products. When the model plant (*Arabidopsis thaliana*) genome sequence was published [40], and the putative UDP-sugar-dependent glycosyltransferase (UGT) genes family was extensively examined the situation altered considerably [41]. The follow-up investigations discovered Arabidopsis UGTs that act on xenobiotics, phytotoxins, phytohormones and polyphenols [42] and also found the first biocatalysts for the terpenoid scaffolds glycosylation [43]. These investigations resulted in the first monoterpenol UGTs isolation as well as characterization of the from: *Vitis vinifera* (grapes) [44], *Actinidia deliciosa* (kiwi) [45] and *Camellia sinensis* (tea) [46-47].

In plant systems, all terpenes classes become glycosylated, influencing their physicochemical characteristics and biological properties [22]. A large number of terpenoid glycoside compounds have been isolated from the plant material and structurally characterized because of their extensive and promising physiological activities. Some terpenoid glycoside compounds are commercialized and sold at high price (Table 2). Glycosylated terpenoid compounds are widely distributed in nature and contain a wide variety of forms because of the combined multitudes of carbohydrates and aglycones [26].

5. Mechanistic Considerations

Nucleophilic displacement is frequently followed S_N1 mechanism (secondary carbon in molecule and weak nucleophiles). The anomeric effect, which favours the formation of α-glycoside compounds, is frequently responsible for the stereochemical glycosylation outcome; however, there are many other factors which influence the new glycosidic bond orientation. Furthermore, competing reactions like migration, orthoesterification, elimination, redox and hydrolysis etc. also complicated the respective process [48-51]. It is well known that 1,2-*trans* glycoside compounds (β-glycosides) can be synthesized easily with the help of the participation of neighboring groups, usually an acyl moiety like pivaloyl, acetyl, phthalimido and benzoyl etc. It has been established that these processes of glycosylation are primarily proceed by a bicyclic intermediate (the acyloxonium cation B) (Scheme 1, Figure:1), which is formed as a result of the departure of the leaving group assisted by a catalyst or promoter, followed by the stabilization of intramolecular carbocation. (**A)**. (Figure 2.2). In this case, a nucleophile (glycosyl acceptor) can only attack the ring from the top face, resulting in stereoselective synthesis of a 1,2-trans glycoside. However, large amounts of 1,2-cislinked products can form occasionally, especially when unreactive alcohols are utilized as substrates. In these cases, glycosylation process is assumed to occur through pathway b (Scheme 1); however, another route for the production of the 1,2 trans glycosidic bond can be considered (pathway a) (Fgure 1). In principle, 1,2-*cis* glycoside compounds(α-glycosides) can be produced having a similar glycosyl donor with a non-participating group (azido, *O*-methyl and *O*-benzyl etc.) at carbon position 2 (C-2). Ideally, S_N2 mechanism followed by leaving group (1,2-*trans* oriented) would result in stereospecific 1,2-*cis* glycoside compounds (Scheme 2, Figure:2). However, as the reaction frequently follows S_N1 mechanism, fairly poor control of stereoselectivity is usually attained Even though, thermodynamically, anomeric product is favourable, a large kinetic b-linked product amount is frequently attained or even preferred because of the irreversible nature of the process of glycosylation of complex aglycones [13].

6. Factors affecting the glycosylation stereoselectivity

Stereoselective synthesis of 1,2-cis glycoside compounds (α-glycosides) is more demanding as compare to the 1,2-trans glycoside compounds (β-glycosides). Whereas the production of 1,2-trans-glycoside compounds is highly favored by the participation of neighboring group atoms, the production of 1,2-cis glycoside compounds also depends on the anomeric effect. The use of substituents which are not participating at carbon-2 is the main strategy for the α-glycosylation. Other concepts of the 1,2-cis glycosylation applied are as follow: (i) leaving group/ promoter-assisted process of glycosylation by means of SN2 mechanism (ii) influence of participating solvent (iii) long-range involvement (iv) steric bulkiness at carbon-6 position of respective carbohydrate compound. These and various other factors like pressure, temperature, position of hydroxyl groups and protecting groups etc. are explained here in detail.

6.1. Glycosyl donor structure

6.1.1. Neighboring group

One of the most important parameters for directing stereoselectivity towards the production of β-glycoside (1,2-trans) linked compound is the participation of neighboring groups. That is why, the major necessity for stereoselective β-glycoside compounds synthesis is the presence of substituents, which do not participate in the reaction, at carbon-2 benzyl (OBn) is the most general used substituent which does not participate in reaction for azide (N_3) and neutral sugars to synthesize 2-amino-2-deoxy sugars. Though, other substances are rarely used like O-methyl (OMe), NO_2, $NHCOCF_3$, $OCOCCl_3$, N-anisylidene ($N{=}CHC_6H_4$-p-OMe). It should be noted that the use of substituents which do not take part in chemical reaction at carbon-2 alone cannot be regarded as a warrant for the effective synthesis of β-glycoside compounds, which obviously depends on several other factors as discussed below.

6.1.2. Leaving groups

There are various papers which deal with the different glycosylation methods comparison applied for specific targets, but only a few concepts can be represented reliably. The activation of halides (chlorides, bromides) using halide ion (e.g., Bu_4NBr) has been unambiguously shown that the highest α/β-glycoside compounds are obtained. However, this method can't be used for the extremely reactive glycosyl halide compounds and limits the use of this method for the complex oligosaccharides synthesis [27]. There is a several publications that report the success of above-described concept. Since the glycosylation reactions take place in various cases by S_N1 mechanism, the leaving group orientation at anomeric center is of less importance. Although, generally the glycosylation reactions occur by S_N2 mechanism, where the anomeric configuration inversion take place. In this context, glycosyl donors with 1,2-cis oriented glycosyl donor form 1,2-trans glycoside compounds: like glycosyl halide compounds with insoluble catalysts, α-imidates using BF_3-Et_2O, Et-ethyl (boron trifluoride etherate) under low temperature, 1,2-anhydro sugars. Conversely, glycosyl donar with 1,2- trans-orientation stereospecifically have the 1,2- cis glycoside compounds, e.g., extremely reactive β-glucosyl halide compounds, anomeric mannosyl triflates and glycosyl thiocyanates produced in situ for β-mannosides synthesis [52].

6.1.3. Protecting groups

The effect on the stereoselectivity is due to the neighbouring group at carbon-2 is of great significant. The other substituents effects are of less significant, but there are some issues which are seemed to be important. Later on, it has been found that stereochemical outcomes of glycosylation process has also affected greatly by the presence of certain moieties at carbon-6 position. It was clearly shown that the 6-O-benzyl group replacement of glucose derivatives with carbamates or esters resulted in the preferential α-glucosides formation [53]. Such findings may be rationalized by the carbon-6 substituent's long-range neighboring group assistance, but there is no strong evidence yet. Strong electron-withdrawing and steric bulkiness properties of substituents present at carbon-6 were also found to be most likely advantageous for α-glucosylation because of the shielding (electronically/ sterically) the top ring face and thus causing the nucleophilic attack from opposite end. For the formation of α-galactosides, diethylthiocarbamoyl, p-methoxybenzoyl substances were therefore observed to be extremely beneficial. Similar effects have also been observed for D-glucose, L-rhamnose and L-fucose derivatives. Interestingly, when strong electron-withdrawing substances (2,2,2-trifluoroethyl, trichloroacetyl, trifluoroacetyl) were present at carbon-4 position compared to 4-O-benzyl, no or very little effect on selectivity was found. The stereoselectivity at anomeric center of the substance can also be strongly influenced by the torsional effects caused by the cyclic acetal protective groups; however, these effects at this point remain somewhat unpredictable [54].

6.1.4. Solvent Effect

The effect of solvent where the reaction take place is also a significant factor that effects the stereoselectivity of the compound at anomeric center of the respective substance. Hence, it has been demonstrated that there are some solvents which are used in the reaction media to carry out respective reaction, have a stereo-directing effect. Polar solvents used in reaction are found to enhance the β-glycoside synthesis rate by decreasing anomeric effect through separation of charge between β-O-1 and O-5. If there is desired to synthesize α-glycoside compounds, toluene, $ClCH_2CH_2Cl$ or CH_2Cl_2, are observed to be suitable solvents. Other strong forces are also considered when using participating solvents than solvolysis. Diethyl ether and acetonitrile were observed to be the limiting cases for α and β-D-glucosides preferential formation, respectively. Conversely, solvents like tetrahydrofuran (THF) or diethyl ether can also take part in the process of glycosylation for different compounds synthesis, but in such cases, equatorial intermediate compounds are preferentially produced, thus causing the axial formation of glycosidic bond. Recently, dioxane was found to be an excellent solvent for the glycosylation process because of its structure in which lone pair present at oxygen atom is easily accessible for participation. For polymer-supported synthesis, the same concepts can be applied to the stereo-directing effects of solvents used in glycosylation processes. Another solvent, nitroethane was also successfully applied for the synthesis of α-glycoside compounds [55].

6.2. Glycosyl acceptor structure

6.2.1. Hydroxyl position

Alcohol reactivity's general concepts are inversely associated with 1,2-cis stereoselectivity. Usually, the lowest ratios of α/β are provided by the most reactive hydroxyl: the stronger the nucleophilic substance, the faster the chemical reaction, and thus the harder it is to regulate. The general rule typically states about sugar or aliphatic glycosyl acceptors: reactions involved in glycosylation process of highly reactive primary hydroxyl usually offers lower stereoselectivity compared to that of secondary hydroxyl. The same concepts apply to glycopeptide synthesis, where threonine secondary hydroxyl glycosylation usually provides higher α-stereoselectivity for the reaction than when the primary serine hydroxide group is glycosylated with trichloroacetimidate or 2-azido-2-deoxy-galactosyl bromide. Sometimes, in contrast to that of the secondary hydroxyls, primary hydroxyls have much higher 1,2-cis stereoselectivity.

6.2.2. Protecting groups

It is well known that electron-withdrawing substituents of ester decrease the neighboring hydroxyl group's electron density by reducing its nucleophilicity. On the one hand, this can increase stereoselectivity, as the chemical reaction may be conducted in a more regulated way, while less reactive hydroxyls, when surrounded by various deactivating substances, may lose their marginal chemical reactivity entirely, resulting in lower yield of glycosides [52]. For example, galactose axial 4-OH glycosylation often provides excellent αstereoselectivity, particularly when combined with substituents having good electron withdrawing capability (O-benzoyl).

6.3. Catalyst addition

For α-glycosylation, milder chemical conditions are usually beneficial. Therefore, chemical reactions catalyzed by halide ions provide best results for the production of glycoside compounds using glycosyl halides as precursor. However, thioglycosides perform in better way with mild promoter activation i.e., iodonium dicollidine perchlorate; while trichloroacetimidates are activated using strong acid catalyst like trifluoromethanesulfonic acid or trimethylsilyl trifluoromethane sulfonate. Furthermore, the stereochemical effect of the process of glycosylation is frequently influenced by the different additions to promoter systems depending on the reaction requirement.

6.4. Pressure and temperature

High pressure given to the reaction media which have participating donors of glycosyl further improves beta selectivity; however, high pressure given to reaction media which does not have participating donor of glycosyl compound, significant increase in reaction yield was observed with only small stereoselectivity changes. Glycosylation process controlled kinetically, usually promote βglycoside compounds production under low temperature. Thus, glycosylation with thioglycosides carried out at room temperature using TMSOTf and PhSeNPhth (Ph-phenyl), produced primarily α-glucoside compounds while β-glucoside compounds were produced almost exclusively at temperature of 318K. Conversely, there have also been observed better 1,2-cis stereo selectivity under low temperature.

6.5. Concentration

The reaction media concentration also affects anomeric selectivity, enhancing the relative product formation rate associated with 1,2-cis; in contrast, dilution significantly delay the chemical reaction, so there is a good balance between efficiency and selectivity always.

7. Biological Activities of terpene glycosides

Terpene glycosides (TGs) have a higher water solubility and more stability as compare to their corresponding aglycone compounds. Despite their lack of odour, monoterpene glycosides are of interest for the industries based on flavour and fragrance because of the possibility of controlled release of bound compounds having aroma. Furthermore, these compounds showed good various biological activities. Hence, monoterpene glycosides are suggested to enhance fragrance cut flowers fragrance to improve smoking cigarettes quality [56], to garmets impregnation, to inhibit unpleasant smell of pet-care and sanitary products, and to mask odor of perspiration. These compounds are also used in oral deodorant to decrease feces odor, in long-lasting deodorants ingredients, in bath preparations and in massage oil ingredients. Incubating skin microflora with several kinds of glycoside compounds revealed the applicability of employing odorless compounds (TGs) as fragrance materials. Most TGs, (especially ß-D-glucosides), were found to be metabolized by skin microbiome thus releasing the aglycone compounds as fragrance materials [57-58]. Glucosidase enzyme extracted from the skin microbiome may also hydrolyze monoterpene glycosides. Besides their function to release fragrance compounds slowly, glycoside compounds also act to release antifungal and antibacterial substances slowly [59]. Monoterpenes have been shown to have antibacterial properties [60]. Decyl glucoside is a nonionic surfactant that is commonly used in cosmetic products and also in those products used for sensitive skin. Many natural personal care companies use this compound because the starting material used for the synthesis is plant-derived and also the synthesized product is biodegradable [61]. Monoterpene glucosides may be used as an alternative surfactant because they have a similar chemical structure and can be synthesized biotechnologically from natural products [12]. Generally, menthol glucoside was detected in the essential oils of various odorous plants especially in *Mentha arvensis.* As discussed above, these glycosides compounds have various properties due to which these compounds have fascinating applications in various industries. But the quantities of these compounds are very low in nature, and there is a need to develop a process for the synthesis of these compounds.

Table 1: List of enzymes used for terpene glycoside production

Sr. No.	Glycoside Product	Enzyme	References
1	Geranyl β-glucoside	*Trichoderma citrinoviride* β-glucosidase	[62]
2	Perillyl alcohol	Almond β-glucosidase	[63]
3	Geranyl β-glucoside	*Arabidopsis thaliana* glucosyltransferase	[64]
4	Geranyl, neryl, citronellyl β-glucoside	*Pichia etchellsii* β-glucosidase	[65]
5	Geranyl, neryl rutinoside	*Acremonium sp.* DSM 24697 α-rhamnosyl-β-glucosidase	[66]]
6	Rebaudioside A	Hydrolase of *Gibberella fujikuroi*	[67]
7	Stevioside α-glucosides	*Bacillus firmus* β-cyclodextrin glucanotransferase	[68]]
8	Stevioside β-galactosides	*Bovine colostrum* β-galactosyltransferase	[69]
9	Asiaticoside β-galactosides	*Bovine colostrum* β-galactosyltransferase	[70]
10	Ginsenoside Rg1 β-galactosides	*Bovine colostrum* β-galactosyltransferase	[71]
11	Geranyl β-glucoside	Almond β-glucosidase	[27]]

Table 2: Market price of some commercialized terpene glycoside compounds

Sr. No.	Products	Source	Price
1	Stevioside	Sigma Aldrich, USA	9452.20$/g
2	Ginsenoside Rb1	Santa Cruz Biotechnology USA	69504.53$/g
3	Glycyrrhizic acid	Sigma Aldrich, USA	3.14$/g
4	Geranyl glucoside	Crbosynth Limited, UK	27435.45$/g
5	Oleanolic acid	Sigma Aldrich, USA	889.74$/g

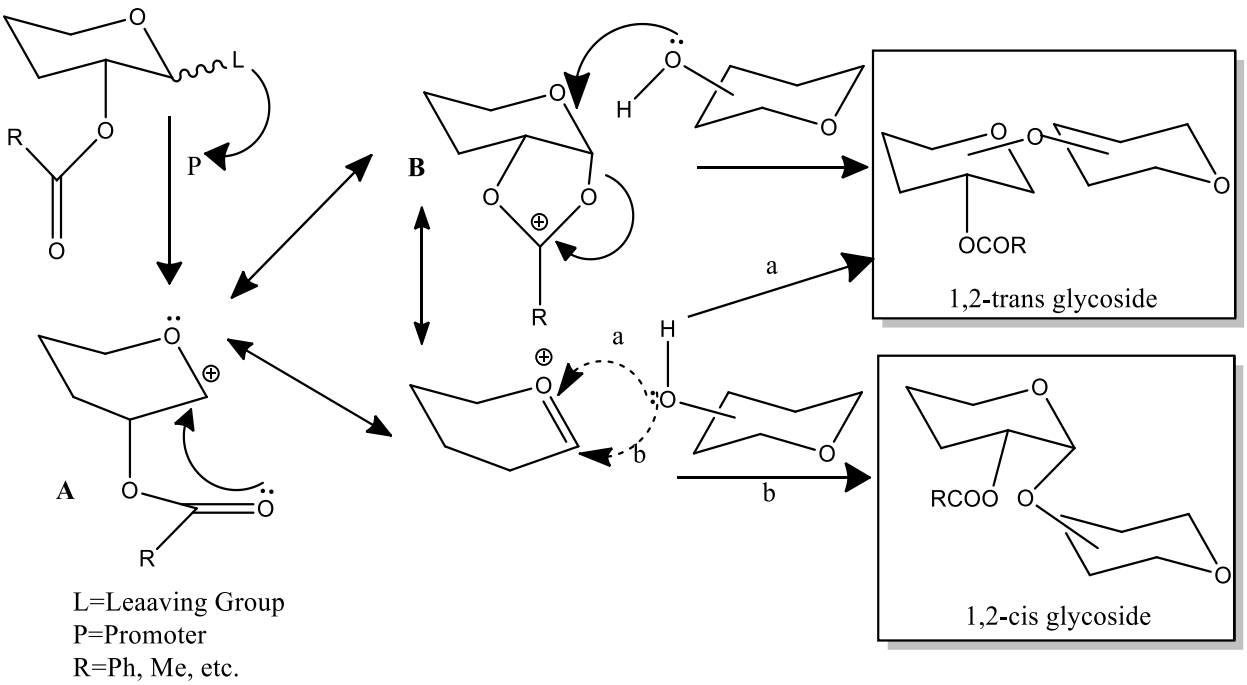
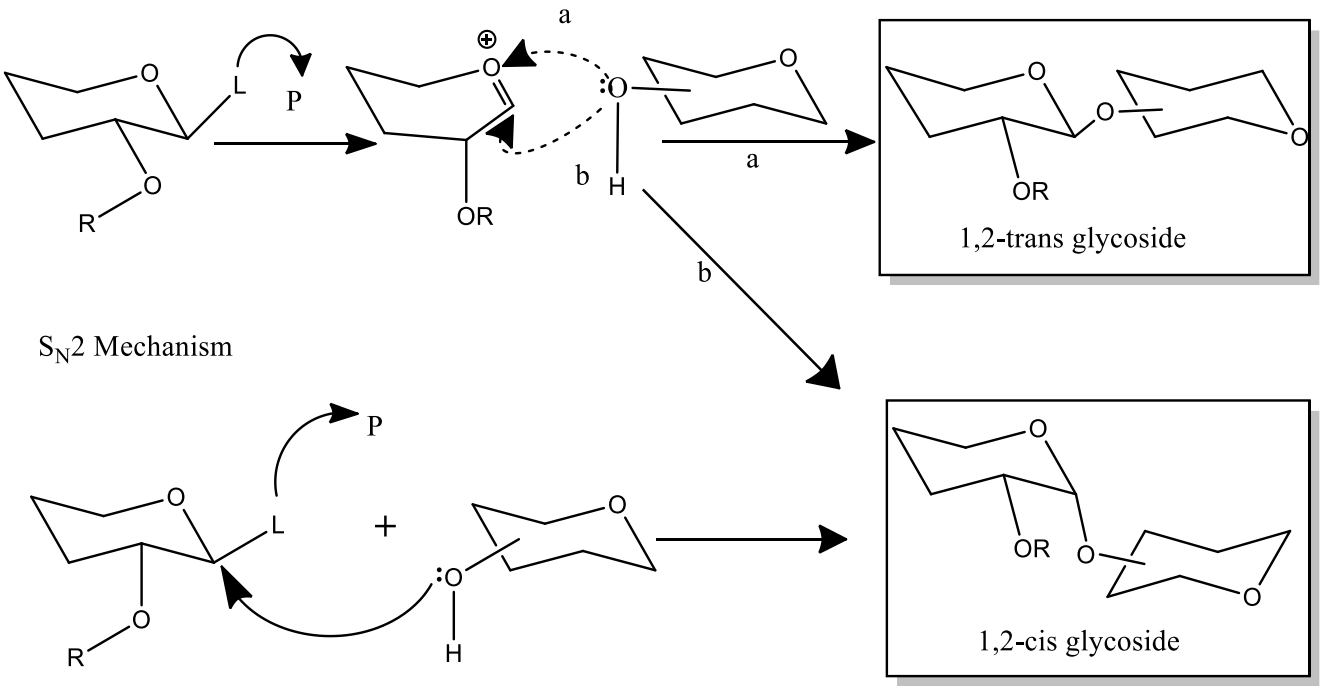


Figure 1: Mechanism of Glycosylation (Scheme 1)

S_N1 Mechanism



S_N2 Mechanism

R= Bn, Me, etc.
L=Leaving group
P=Promotor

Figure 2: mechanism of Glycosylation (Scheme 2)

8. Conclusion

Besides cooling effect, menthol possesses a variety of biological activities, including antifungal, analgesic, anticancer, antibacterial, antiviral, anti-inflammatory, insecticidal and antitussive actions. Menthol has proven to be one of those effective terpenes who used for enhancing the pharmaceuticals dermal penetration. Despite these benefits associated with the use of menthol, there are various drawbacks like low water solubility, high volatility and strong minty smell. These drawbacks can be overcome by the modification of menthol into respective compounds. However, isolation of Imenthol glycoside from the mint plant revealed that this compound has good water solubility and also little capability to sublimate after storage. Hence, research on the impact of menthol glycosides on various biological properties is of interest. From the above discussion, it can be concluded that terpene alcohols are released easily from their respective glycosidic precursors through enzymatic or acidic hydrolysis. This delayed and controlled release mechanism of the fragrance and aroma has a fascinating industrial potential. Many therapeutically important drugs involved glycosylated natural compounds in which the carbohydrate residues are bonded to those natural compounds which are vital for the respective biological activity. Moreover, the precise sequence and identity of the glycosyl moieties affect the drug's pharmacology/pharmacokinetics, which also evaluate the biological selectivity at the organism, tissue and molecular level, and also decide their mode of action.

References

[1] S. Nisar, M.A. Hanif, M. Zahid, A. Ghaffar. (2022). Enzymatic glycosylation of menthol: optimization of synthesis and extraction processes using response surface methodology and biological evaluation of synthesized product. Chemical Papers. 76(5): 2649-2675.

[2] I. Batool, S. Nisar, L. Hamrouni, M.I. Jilani. (2018). Extraction, production and analysis techniques for menthol: a review. International Journal of Chemical and Biochemical Sciences. 14: 71-76.

[3] T. Patel, Y. Ishiuji, G. Yosipovitch. (2007). Menthol: a refreshing look at this ancient compound. Journal of the American Academy of Dermatology. 57(5): 873-878.

[4] G.P. Kamatou, I. Vermaak, A.M. Viljoen, B.M. Lawrence. (2013). Menthol: a simple monoterpene with remarkable biological properties. Phytochemistry. 96: 15-25.

[5] M. Oz, E.G. El Nebrisi, K.-H.S. Yang, F.C. Howarth, L.T. Al Kury. (2017). Cellular and molecular targets of menthol actions. Frontiers in pharmacology. 8: 472.

[6] I. Sakata, H. Iwamura. (1979). Synthesis and properties of menthyl glycosides. Agricultural and Biological Chemistry. 43(2): 307-312.

[7] K. Ide, T. Sato, J. Aoi, H. Do, K. Kobayashi, Y. Honda, K. Kirimura. (2013). l-Menthyl α-Maltoside as a Novel Low-molecular-weight Gelator. Chemistry Letters. 42(6): 657-659.

[8] F. De Bruyn, J. Maertens, J. Beauprez, W. Soetaert, M. De Mey. (2015). Biotechnological advances in UDP-sugar based glycosylation of small molecules. Biotechnology Advances. 33(2): 288-302.

[9] K. Schmölzer, A. Gutmann, M. Diricks, T. Desmet, B. Nidetzky. (2016). Sucrose synthase: A unique glycosyltransferase for biocatalytic glycosylation process development. Biotechnology Advances. 34(2): 88-111.

[10] A.V. Demchenko. (2008). General aspects of the glycosidic bond formation. Handbook of Chemical Glycosylation. 9: 1-27.

[11] V. Křen, J. Thiem. (1997). Glycosylation employing bio-systems: from enzymes to whole cells. Chemical Society Reviews. 26(6): 463-473.

[12] W. Schwab, T. Fischer, M. Wüst. (2015). Terpene glucoside production: improved biocatalytic processes using glycosyltransferases. Engineering in Life Sciences. 15(4): 376-386.

[13] A.V. Demchenko. (2003). Stereoselective chemical 1, 2-cis O-glycosylation: from 'sugar ray'to modern techniques of the 21st century. Synlett. 2003(09): 1225-1240.

[14] J. Masteli, I. Jerkovi, M. Vinkovi. (2004). Synthesis ofselected naturally occurring glucosides of volatile com-pounds. Their chromatographic and spectroscopic properties. Croatica Chemica Acta.

[15] G. Desmares, D. Lefebvre, G. Renevret, C.L. Drian. (2001). Selective Formation of β-D-Glucosides of Hindered Alcohols. Helvetica Chimica Acta. 84(4): 880-889.

[16] R.W. Gantt, P. Peltier-Pain, J.S. Thorson. (2011). Enzymatic methods for glyco (diversification/randomization) of drugs and small molecules. Natural product reports. 28(11): 1811-1853.

[17] A. Chang, S. Singh, G.N. Phillips Jr, J.S. Thorson. (2011). Glycosyltransferase structural biology and its role in the design of catalysts for glycosylation. Current opinion in biotechnology. 22(6): 800-808.

[18] G.J. Williams, C. Zhang, J.S. Thorson. (2007). Expanding the promiscuity of a natural-product glycosyltransferase by directed evolution. Nature chemical biology. 3(10): 657-662.

[19] R.W. Gantt, P. Peltier-Pain, W.J. Cournoyer, J.S. Thorson. (2011). Using simple donors to drive the equilibria of glycosyltransferase-catalyzed reactions. Nature chemical biology. 7(10): 685-691.

[20] T. Desmet, W. Soetaert. (2011). Enzymatic glycosyl transfer: mechanisms and applications. Biocatalysis and Biotransformation. 29(1): 1-18.

[21] J.P. Rasor, E. Voss. (2001). Enzyme-catalyzed processes in pharmaceutical industry. Applied Catalysis A: General. 221(1-2): 145-158.

[22] F. Rivas, A. Parra, A. Martinez, A. Garcia-Granados. (2013). Enzymatic glycosylation of terpenoids. Phytochemistry reviews. 12(2): 327-339.

[23] E. Brenna, C. Fuganti, S. Serra. (2003). Enantioselective perception of chiral odorants. Tetrahedron: asymmetry. 14(1): 1-42.

[24] P.S. Cheetham, Combining the technical push and the business pull for natural flavours. In

Biotechnology of aroma compounds, Springer: 1997; pp 1-49.
[25] R.G. BERGER. (1997). Biotechnology of aroma compounds. Advances in biochemical engineering, biotechnology. 55.
[26] W. Schwab, R. Davidovich-Rikanati, E. Lewinsohn. (2008). Biosynthesis of plant-derived flavor compounds. The plant journal. 54(4): 712-732.
[27] B.M.d. Roode, L. Oliehoek, A. van der Padt, M.C. Franssen, R.M. Boom. (2001). Downstream processing of enzymatically produced geranyl glucoside. Biotechnology progress. 17(5): 881-886.
[28] T. Ojima. Studies on enzymatic synthesis of functional sugars. School of Bioagricultural Sciences, Nagoya University, 2013.
[29] V. Kren, L. Martínková. (2001). Glycosides in medicine:"The role of glycosidic residue in biological activity". Current medicinal chemistry. 8(11): 1303-1328.
[30] T. Murata, T. Usui. (2006). Enzymatic synthesis of oligosaccharides and neoglycoconjugates. Bioscience, biotechnology, and biochemistry. 70(5): 1049-1059.
[31] H. Nakagawa, Y. Dobashi, T. Sato, K. Yoshida, T. Tsugane, S. Shimura, K. Kirimura, K. Kino, S. Usami. (2000). α-Anomer-selective glucosylation of menthol with high yield through a crystal accumulation reaction using lyophilized cells of Xanthomonas campestris WU-9701. Journal of bioscience and bioengineering. 89(2): 138-144.
[32] J. Kurosu, T. Sato, K. Yoshida, T. Tsugane, S. Shimura, K. Kirimura, K. Kino, S. Usami. (2002). Enzymatic synthesis of α-arbutin by α-anomer-selective glucosylation of hydroquinone using lyophilized cells of Xanthomonas campestris WU-9701. Journal of bioscience and bioengineering. 93(3): 328-330.
[33] L. Guo, X. Chen, L. Xu, M. Xiao, L. Lu. (2018). Enzymatic synthesis of 6′-sialyllactose, a dominant sialylated human milk oligosaccharide, by a novel exo-α-sialidase from Bacteroides fragilis NCTC9343. Applied and environmental microbiology. 84(13): e00071-18.
[34] R. Santamaria, G. Del Rio, G. Saab, M. Rodriguez, X. Soberon, A. López-Munguía. (1999). Alcoholysis reactions from starch with α-amylases. FEBS letters. 452(3): 346-350.
[35] M. Francis, C. Allcock. (1969). Geraniol β-D-glucoside; occurrence and synthesis in rose flowers. Phytochemistry. 8(8): 1339-1347.
[36] E. Stahl-Biskup. (1987). Monoterpene glycosides, state-of-the-art. Flavour and Fragrance Journal. 2(2): 75-82.
[37] P. Winterhalter, G.K. Skouroumounis. (1997). Glycoconjugated aroma compounds: occurrence, role and biotechnological transformation. Biotechnology of aroma compounds. 73-105.
[38] R. Cordonnier, C. Bayonove. (1974). Mise en évidence dans la baie de raisin, variété Muscat d'Alexandrie, de monoterpènes liés révélables par une ou plusieurs enzymes du fruit. CR Acad. Sci. Paris. 278: 3387-3390.
[39] P.J. Williams, C.R. Strauss, B. Wilson, R.A. Massy-Westropp. (1982). Novel monoterpene disaccharide glycosides of Vitis vinifera grapes and wines. Phytochemistry. 21(8): 2013-2020.
[40] S. Kaul, H.L. Koo, J. Jenkins, M. Rizzo, T. Rooney, L.J. Tallon, T. Feldblyum, W. Nierman, M.-I. Benito, X. Lin. (2000). Analysis of the genome sequence of the flowering plant Arabidopsis thaliana. nature. 408(6814): 796-815.
[41] Y. Li, S. Baldauf, E.-K. Lim, D.J. Bowles. (2001). Phylogenetic Analysis of the UDP-glycosyltransferase Multigene Family of Arabidopsis thaliana* 210. Journal of Biological Chemistry. 276(6): 4338-4343.
[42] D. Bowles, J. Isayenkova, E.-K. Lim, B. Poppenberger. (2005). Glycosyltransferases: managers of small molecules. Current opinion in plant biology. 8(3): 254-263.
[43] L. Caputi, M. Malnoy, V. Goremykin, S. Nikiforova, S. Martens. (2012). A genome-wide phylogenetic reconstruction of family 1 UDP-glycosyltransferases revealed the expansion of the family during the adaptation of plants to life on land. The Plant Journal. 69(6): 1030-1042.
[44] F. Bönisch, J. Frotscher, S. Stanitzek, E. Rühl, M. Wüst, O. Bitz, W. Schwab. (2014). A UDP-glucose: monoterpenol glucosyltransferase adds to the chemical diversity of the grapevine metabolome. Plant Physiology. 165(2): 561-581.
[45] Y.K. Yauk, C. Ged, M.Y. Wang, A.J. Matich, L. Tessarotto, J.M. Cooney, C. Chervin, R.G. Atkinson. (2014). Manipulation of flavour and aroma compound sequestration and release using a glycosyltransferase with specificity for terpene alcohols. The Plant Journal. 80(2): 317-330.
[46] S. Ohgami, E. Ono, M. Horikawa, J. Murata, K. Totsuka, H. Toyonaga, Y. Ohba, H. Dohra, T. Asai, K. Matsui. (2015). Volatile glycosylation in tea plants: Sequential glycosylations for the biosynthesis of aroma β-primeverosides are catalyzed by two Camellia sinensis glycosyltransferases. Plant Physiology. 168(2): 464-477.
[47] C. Song, K. Härtl, K. McGraphery, T. Hoffmann, W. Schwab. (2018). Attractive but toxic: emerging roles of glycosidically bound volatiles and glycosyltransferases involved in their formation. Molecular plant. 11(10): 1225-1236.
[48] H.M. Osborn, T.H. Khan. (2000). Oligosaccharides: their synthesis and biological roles. Oxford University Press on Demand: pp.
[49] C.J. Knill, J.F. Kennedy, Lindhorst, TK, Essentials of carbohydrate chemistry and biochemistry , Wiley-VCH, Weinheim, Germany, 2007 (xiii+ 317 pp.,£ 45.00, ISBN 3-527-31528-4). In Elsevier: 2009.
[50] R.V. Stick. (2001). Carbohydrates: the sweet molecules of life. Elsevier: pp.
[51] G. Boons, K. Hale. (2000). Functionalised saccharides. Organic Synthesis with Carbohydrates. 56-102.
[52] D. Crich, M. Smith. (2000). S-(4-Methoxyphenyl) benzenethiosulfinate

(MPBT)/trifluoromethanesulfonic anhydride: a convenient system for the generation of glycosyl triflates from thioglycosides. Organic letters. 2(25): 4067-4069.

[53] T. Mukaiyama, M. Suenaga, H. Chiba, H. Jona. (2002). Highly α-selective glycosylation with glycopyranosyl fluorides having diethylthiocarbamoyl group. Chemistry letters. 31(1): 56-57.

[54] G. Anilkumar, L.G. Nair, L. Olsson, J.K. Daniels, B. Fraser-Reid. (2000). α-Glucosaminide synthesis: exercising stereocontrol at C1 or C2 via torsional effects or DeShong nucleophiles. Tetrahedron Letters. 41(40): 7605-7608.

[55] A.V. Demchenko. (2003). 1, 2-cis O-Glycosylation: methods, strategies, principles. Current organic chemistry. 7(1): 35-79.

[56] X. Bai, D. Mou, W. Dong, G. Peng, R. Gong, L. Wang, Y. Zhang. (2012). Method for compensating flavor of low tar cigarettes. From Faming Zhuanli Shenqing, CN. 102423114.

[57] T. Ikemoto, B.I. Okabe, K. Mimura, T. Kitahara. (2002). Formation of fragrance materials from odourless glycosidically-bound volatiles by skin microflora (Part 1). Flavour and Fragrance Journal. 17(6): 452-455.

[58] T. Ikemoto, K. Mimura, T. Kitahara. (2003). Formation of fragrant materials from odourless glycosidically-bound volatiles on skin microflora (Part 2). Flavour and Fragrance Journal. 18(1): 45-47.

[59] S.H. Duncan, E.C.M. Leitch, K.N. Stanley, A.J. Richardson, R.A. Laven, H.J. Flint, C.S. Stewart. (2004). Effects of esculin and esculetin on the survival of Escherichia coli O157 in human faecal slurries, continuous-flow simulations of the rumen and colon and in calves. British journal of nutrition. 91(5): 749-755.

[60] E. Schmidt, J. Wanner, M. Höferl, L. Jirovetz, G. Buchbauer, V. Gochev, T. Girova, A. Stoyanova, M. Geissler. (2012). Chemical composition, olfactory analysis and antibacterial activity of Thymus vulgaris chemotypes geraniol, 4-thujanol/terpinen-4-ol, thymol and linalool cultivated in southern France. Natural Product Communications. 7(8): 1934578X1200700833.

[61] M.Y. Rather, S. Mishra. (2013). β-Glycosidases: an alternative enzyme based method for synthesis of alkyl-glycosides. Sustainable Chemical Processes. 1(1): 1-15.

[62] M. Chandra, A. Kalra, N.S. Sangwan, R.S. Sangwan. (2013). Biochemical and proteomic characterization of a novel extracellular β-glucosidase from Trichoderma citrinoviride. Molecular biotechnology. 53(3): 289-299.

[63] E. Xanthakis, S. Magkouta, H. Loutrari, H. Stamatis, C. Roussos, F.N. Kolisis. (2009). Enzymatic synthesis of perillyl alcohol derivatives and investigation of their antiproliferative activity. Biocatalysis and Biotransformation. 27(3): 170-178.

[64] L. Caputi, E.K. Lim, D.J. Bowles. (2008). Discovery of new biocatalysts for the glycosylation of terpenoid scaffolds. Chemistry–A European Journal. 14(22): 6656-6662.

[65] P. Bachhawat, S. Mishra, Y. Bhatia, V. Bisaria. (2004). Enzymatic synthesis of oligosaccharides, alkyl and terpenyl glucosides, by recombinant Escherichia coli-expressed Pichia etchellsii β-glucosidase II. Applied biochemistry and biotechnology. 118(1): 269-282.

[66] M. Minig, L.S. Mazzaferro, R. Erra-Balsells, G. Petroselli, J.D. Breccia. (2011). α-Rhamnosyl-β-glucosidase-catalyzed reactions for analysis and biotransformations of plant-based foods. Journal of agricultural and food chemistry. 59(20): 11238-11243.

[67] B.H. de Oliveira, J.F. Packer, M. Chimelli, D.A. de Jesus. (2007). Enzymatic modification of stevioside by cell-free extract of Gibberella fujikuroi. Journal of biotechnology. 131(1): 92-96.

[68] V. Jaitak, V.K. Kaul, N. Kumar, B. Singh, L. Savergave, V. Jogdand, S. Nene. (2009). Simple and efficient enzymatic transglycosylation of stevioside by β-cyclodextrin glucanotransferase from Bacillus firmus. Biotechnology letters. 31(9): 1415-1420.

[69] B. Danieli, M. Luisetti, M. Schubert-Zsilavecz, W. Likussar, S. Steurer, S. Riva, D. Monti, J. Reiner. (1997). Regioselective Enzyme-Mediated Glycosylation of Natural Polyhydroxy Compounds. Part 1. Galactosylation of stevioside and steviolbioside. Helvetica chimica acta. 80(4): 1153-1160.

[70] D. Monti, A. Candido, M.M. Cruz Silva, V. Křen, S. Riva, B. Danieli. (2005). Biocatalyzed generation of molecular diversity: selective modification of the saponin asiaticoside. Advanced Synthesis & Catalysis. 347(7-8): 1168-1174.

[71] B. Danieli, L. Falcone, D. Monti, S. Riva, S. Gebhardt, M. Schubert-Zsilavecz. (2001). Regioselective Enzymatic Glycosylation of Natural Polyhydroxylated Compounds: Galactosylation and Glucosylation of Protopanaxatriol Ginsenosides1. The Journal of organic chemistry. 66(1): 262-269.