Abstract

Introduction: Galactosemia describes four diseases resulting from mutations in genes which code for enzymes involved in the metabolism of galactose and its derivatives. It has a wide range of symptoms ranging from the relatively mild (early onset cataracts) to severe damage to the liver, brain and ovaries which results in significant physical and cognitive disability. The only treatment is the removal or reduction of galactose in the diet. This treatment is unsatisfactory, particularly in the most severe forms of the disease. Considerable research efforts are being made to develop specific therapies for galactosemia. These include gene therapies, pharmacological chaperones, drugs to block the production of potentially toxic metabolites and enzyme replacement therapy. However, these are unlikely to be translated into the clinic for at least a decade.

Areas covered: This review considers existing drugs, nutrients and treatments which could be relatively rapidly repurposed for the treatment of galactosemia. If successful, these would enable an improvement in the prognosis for galactosemia patients.

Expert opinion: Dietary antioxidants which are already widely used and generally considered safe (e.g. resveratrol, purple sweet potato colour) should be tested for their efficacy in galactosemia. Pharmaceutical antioxidants (e.g. idebenone) should also be considered. Phosphate supplementation, along with careful monitoring of phosphate levels in the patient's diet should also be considered. Efforts to develop specific therapies for galactosemia should continue.

Keywords: dietary antioxidant; idebenone; inherited metabolic disease; phosphate supplementation; purple sweet potato colour; resveratrol

Highlights

- Galactosemia describes four inherited metabolic diseases of galactose metabolism
- Current treatments for galactosemia are inadequate
- Dietary antioxidants such as resveratrol may be useful in the treatment of galactosemia
- Phosphate supplementation should be considered in galactosemic patients
- eIF2α Phosphatase inhibitors may be useful to reduce premature ovarian insufficiency
- Efforts to develop more specific therapies for this disease should continue

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1. Introduction

Galactosemia is a term which describes four diseases resulting from mutations in the genes encoding enzymes of galactose metabolism [1,2]. The Leloir pathway facilitates the conversion of galactose to the glycolytic intermediate glucose 6-phosphate (Figure 1) [3]. It is also important in the synthesis of UDP-sugars, which are important precursors for the synthesis of glycolipids and glycoproteins. The disaccharide lactose is a significant source of galactose in the diets of babies and Caucasian adults. This disaccharide, which occurs in milk, is hydrolysed releasing D-glucose and β-D-galactose. In aqueous solution, the two anomers of D-galactose (α-D-galactose and β-D-galactose) interconvert at an appreciable rate [4]. However, this rate is not enough to supply the Leloir pathway whose first enzyme, galactokinase (GALK1; EC 2.7.1.6), only recognises the α-anomer of D-galactose. Galactose mutarotase (aldose 1-epimerase, GALM; EC 5.1.3.3) catalyses the interconversion of the D-galactose anomers [5,6]. Mutations in the *GALM* gene can result in the most recently discovered form of the disease, Type IV galactosemia, which appears to behave more like a complex genetic disorder than a simple, Mendelian disease [7,8]. The Leloir pathway is generally considered to begin with the phosphorylation of α-D-galactose at the expense of ATP in a reaction catalysed by galactokinase [9,10]. Type II galactosemia (OMIM #230200) is caused by mutations in the *GALK1* gene [11,12]. The product of this reaction α-D-galactose 1-phosphate participates in an exchange reaction with UDP-glucose, generating α-D-glucose 1-phosphate and UDP-galactose. This reaction is catalysed by galactose 1-phosphate uridylyltranferase (GALT; EC 2.7.7.10) and mutations in the corresponding gene are associated with type I galactosemia (or classic galactosemia; OMIM #230400) [13-15]. UDP-glucose is regenerated in an isomerisation reaction catalysed by UDP-galactose 4'-epimerase (GALE; EC 5.1.3.2). This enzyme can also catalyse the epimerisation of the *N*-acetyl derivatives of D-glucose and D-galactose [16]. Type III galactosemia (OMIM #230350) is caused by mutations in the *GALE* gene [17,18]. The production of α-D-glucose 1-phosphate is generally considered to complete the Leloir pathway. However, one final reaction is required before the carbon atoms in the original galactose molecule can enter glycolysis: α-D-glucose 1-phosphate is isomerised to D-glucose 6-

phosphate in a reaction catalysed by phosphoglucomutase (PGM; EC 5.4.2.2) [19]. To date, no form of galactosemia has been associated with this enzyme. However, congenital disorder of glycosylation, type It (OMIM #614921) is associated with PGM1 deficiency. The glycosylation disorders have some similarity with those seen in galactosemia types I and III [20].

The symptoms of galactosemia are highly variable [21-25]. The most severe forms result in significant cognitive and physical disability in childhood and can result in death of the infant if untreated. The mildest forms result in perturbations of blood chemistry which are not currently associated with any adverse effects on the patient. Almost all forms, except the very mildest, result in childhood onset cataracts. These result from the build-up of galactose in the lens. This is converted to the sugar alcohol galactitol (dulcitol) by the action of aldose reductase (EC 1.1.1.21). Unlike galactose, galactitol cannot be transported across the cell membrane and thus accumulates in the lens cells, upsetting the osmotic balance of these cells [26]. The most severe symptoms are associated with type I and some instances of type III galactosemia. Type III galactosemia probably has the widest phenotypic range [27]. In addition to severely disabling and life-threatening outcomes, it can also result in very mild symptoms which cause little of no harm. Types II and IV have similar symptoms. Typically patients with these types of galactosemia have early onset cataracts, normally in early childhood [8,28,29]. The severity of the symptoms depend on the exact mutation(s) present in the patient along with the patient's environment. In this context, the environment includes the health care available to the patient: early identification of the disease and intervention can slow or prevent the development of some symptoms.

The only recognised treatment for all types of galactosemia is the exclusion, or reduction, of galactose from the diet [21]. There is currently considerable debate about the necessity for strictness in the dietary regime, particularly in adult patients [30]. Despite the potentially devastating symptoms of type I galactosemia, a number of patients have recently been reported to

maintain levels of cognitive function sufficient to enable them to graduate with university degrees [31].

The molecular and cellular pathology of galactosemia is not well understood, except for the development of cataracts (see above). This lack of understanding hinders attempts to develop more effective treatments. In affected individuals, the liver, brain and ovaries are often the most affected organs [21,32]. Movement disorders have been reported in some patients [33]. The liver is the main site for the Leloir pathway and it is believed that the accumulation of galactose 1-phosphate is toxic to cells. The mechanism of this toxicity has not been definitively determined. It should also be noted that galactose itself is toxic at higher concentrations (>5 mM) and several studies have demonstrated that the administration of high levels of galactose to healthy animals results in similar pathology to galactosemia [34,35]. Disturbances in glycoprotein and glycolipid synthesis may partly explain the effects on the brain and ovaries [36,37]. Increased cellular free radical load is also associated with the galactosemic phenotype [38]. This is likely to represent a secondary consequence of metabolic disturbances which then causes further, non-specific damage to cellular components.

While the dietary restriction of galactose is helpful in most patients, it often only slows and reduces the severity of the symptoms. Even with a galactose restricted diet many patients suffer physical and mental disability [39]. A number of other therapies have been proposed [40]. These include the inhibition of GALK1. While this would, presumably, cause similar symptoms to type II galactosemia, it would prevent the build-up of galactose 1-phosphate which is thought to be responsible for some of the more severe pathology in types I and III [29,41]. A number of effective and selective inhibitors have been identified, but none are in clinical use yet [41]. Enzyme replacement therapy works by delivering pure, recombinant enzyme to the affected tissues. In theory, this could be applied in galactosemia. However, it may be necessary to overcome delivery problems to the brain where the blood-brain barrier typically prevents the passage of larger molecules like proteins. Gene therapy is

also possible in theory, but again there may be a need to deliver larger hydrophilic molecules across the blood brain barrier in order to restore activity in this organ. Since many of the disease-associated variants of GALT, GALK1, GALE and GALM are less thermally stable than the wild-type protein, small molecule pharmacological chaperones could be deployed to assist their folding and increase enzymatic activity [8,42-44]. To date, no suitable molecules have been reported, although a promising binding site in GALT has been identified by *in silico* methods [40,42]. All these approaches have considerable promise. Most would all wholly or partly restore the activity of the affected enzyme and, presumably, alleviate the majority of the symptoms. However, they are all many years from being implemented in patients. Considerable basic science work is required on all these approaches before the lengthy process of clinical trials and gaining regulatory approval could begin. This review focuses on existing drugs (and drug-like molecules) which might be redeployed to treat galactosemia.

2. Antioxidants - dietary

Since oxidative stress has been identified as a common occurrence in cells from galctosemic patients and in animal models of galactosemia, it has been suggested that reducing this stress may have benefit to patients [38,45]. This proposition is also supported by animal studies on galactose toxicity. Injection of galactose into rat cerebellums caused an increase in reactive oxygen species, damage to proteins and reduction in cognitive function. These effects were suppressed by the co-administration of the antioxidants ascorbic acid (vitamin C; CAS: 50-81-7; Figure 2) or α-tocopherol (vitamin E; CAS: 59-02-9; Figure 2) [35]. Ascorbate and the plant-derived xanthanoid α-mangostin (CAS: 6147-11-1; Figure 2) protected against oxidative stress and reduced the severity of the galactosemia-like phenotype in a *Drosophila melanogaster* model of the disease [38]. A number plant extracts and plant-derived compounds have been shown to have similar effects in animals exposed to excess galactose. Particularly impressive results have been obtained with purple sweet

potato colour, an extract containing anthocyanins and phenolic compounds [46-50]. In parallel to oxidative stress, high galactose concentrations induce cellular senescence, a condition in which cells permanently cease to divide without undergoing any form of cell death [51]. Some antioxidant compounds, for example the plant alkaloid matrine (CAS: 519-02-8; Figure 2), inhibit the induction of senescence in animal models of galactose toxicity [52].

The ideal dietary antioxidant to use in galactosemia would be readily available, safe to use for extended periods, cross the blood-brain barrier and would combine free radical quenching properties with anti-senescent activity. Purple sweet potato extracts, along with drinks derived from this vegetable are widely consumed in Japan with no significant ill-effects reported [53,54]. The anthocyanins in the extract are known to be absorbed by mammals and to increase antioxidant activity in the blood plasma [55]. There is also some evidence that it inhibits senescence [56]. The combination of these two effects would make purple sweet potato colour potentially attractive as a therapy for galactosemia [57].

Resveratrol (CAS: 501-36-0; Figure 2), a stillbenoid found in grapes and other fruits, also protects against galactose toxicity, partly by reducing oxidative stress [58]. In addition to its antioxidant activity, resveratrol has several protein targets. These include inhibition of NRH-quinone oxidoreductase 2 (NQO2) and activation of the histone deacetylase sirtuin-1 (SIRT-1) [59,60]. It is considered generally safe, with minimal side-effects at doses up to several hundred milligrams per day [61]. There are some concerns that doses in the grams per day range may be harmful and, as will all drugs, interactions with other drugs and inhibition of the cytochrome P450 system should be considered [61-63]. Resveratrol also demonstrates impressive anti-senescent effects. Not only does it inhibit senescence, but can also reverse the process through modulation of RNA splicing. This enables cells to exit from senescence, increase telomere length and resume proliferation [64]. It is known to cross the blood-brain barrier and has been proposed as a treatment for some neurological diseases [65,66]. These combined properties make resveratrol an attractive proposition for use in

galactosemia patients. However, other dietary antioxidants may also be effective; further testing may help determine which are the most promising for clinical trials. The recent development of a credible mouse model for type I galactosemia could help with this, and other evaluations of possible treatments [67]. Even before such results are available, it should be noted that high antioxidant diets are generally considered to deliver a range of health benefits [68]. Therefore, there would be little risk and some potential benefit in recommending such diets to galactosemia patients.

3. Antioxidants – pharmaceutical

Manganese containing porphyrins with antioxidant activity has been used to ameliorate the galactosemic phenotype in a *D. melanogaster* model of the disease [69]. These compounds, which were developed by Aeolus Pharmaceuticals, mimic the activity of the enzyme superoxide dismutase (EC 1.15.1.1), catalysing the reduction of reactive oxygen species. They have been suggested for treatments in a wide range of diseases, including cancers, strokes, radiation injury, amyotrophic lateral sclerosis and diabetes [70]. Mouse model studies showed significant promise for one of these compounds (MnTDE-2-ImP^{5+}; AEOL-10150; CAS: 286475-30-7; Figure 3) in amyotrophic lateral sclerosis and human clinical trials were initiated [71]. However, this compound is not currently used for this disease. It has been granted orphan drug status for the treatment of idiopathic pulmonary fibrosis [72]. Despite the compound's relatively large size, it crosses the blood-brain barrier and it also appears to have relatively low toxicity in humans [70]. The compound used in the galactosemia study was slightly different (MnTE-2-PyP^{5+}; AEOL-10113; CAS: 219818-60-7; Figure 3). However, the promising results of this group of compounds in radiation protection and idiopathic pulmonary fibrosis suggest that clinical trials for galactosemia would be warranted, particularly for MnTE-2-PyP^{5+}.

Antioxidants are used in other genetic diseases. Idebenone (CAS: 58186-27-9; Figure 3), is a coenzyme Q_{10} (CoQ; ubiquinone; CAS: 303-98-0) mimic developed by the Takeda Pharmaceutical Company. It is used in the treatment of

4. Phosphate supplementation

Types I and III galactosemia result in a cellular build-up of galactose 1-phosphate. This molecule is considered to be toxic to cells, although no molecular target(s) have been conclusively identified. Another detrimental effect of the accumulation of this compound is the reduction in the amount of phosphate available to other metabolic processes. Phosphate is essential for energy metabolism involving ATP, the synthesis of nucleic acids and phospholipids, and the control of protein activity by phosphorylation. Disruption of any of these processes is likely to be detrimental to the cell and the organism.

Deletion of the gene encoding GALT in budding yeast *Saccharomyces cerevisiae* (*GAL7*) resulted in depletion in cellular inorganic phosphate levels [84]. Similar effects have been observed in the serum of patients with galactosemia and hereditary frustose intolerance (OMIM #229600), another disease which results in the accumulation of a sugar phosphate [85]. In the yeast model, this phosphate depletion resulted in altered glycogen metabolism, presumably because phosphate ions are required for the enzymatic breaking of α(1→4) glycosidic bonds in this polysaccharide. Reversal of phosphate depletion either by deletion of the galactokinase gene (*GAL1*) or supplementation of the media with phosphate ions prevented the reduction of cellular phosphate levels and restored normal glycogen metabolism [84]. This suggests that phosphate supplementation in galactosemia patients would be worth investigating.

Phosphate supplementation is already used in a variety of conditions, including the treatment of some alcoholics and patients undergoing renal dialysis or kidney transplants, diabetic ketoacidosis,

burns and sepsis [86]. It is generally considered safe, although care needs to be taken if some other medicines are being used at the same time [87,88]. Pharmaceutical preparations already exist in both dissolvable tablets and injectable forms. Therefore the investigation of phosphate supplementation as a possible therapy for galactosemia may prove fruitful and is unlikely to present significant risks to patients. It should also be noted that milk (and milk products) are good sources of dietary phosphate [89]. These are, of course, eliminated or substantially reduced in the galactosemic diet. Therefore, it may be the case that some patients are on reduced phosphate intake diets which would further reduce the availability of phosphate in their cells.

5. Treatment of movement disorders in galactosemia

Movement disorders occur in some patients with type I galactosemia [33]. Dystonia (sustained, uncontrolled muscle contractions is the most commonly observed symptom and weaknesses which results in reduced dexterity and balance is also seen [33,90]. Treatment is not always given, although patients are often supported by physiotherapy and occupational therapy. One patient has been reported to have been treated with trihexyphenidyl (CAS: 144-11-6; Figure 4) and botulinum toxin in addition to a lycra suit [33]. Trihexyphenidyl is used in the treatment of Parkinson's disease and other conditions which result in involuntary movements and botulinum toxin is used as a muscle relaxant in a variety of diseases. Wider consideration of the use of existing drugs to treat dystonia and ataxia may be worth considering for galactosemia patients.

The molecular causes of these movement disorders remain unknown. Work on the *D. melanogaster* model suggests that galactose 1-phosphate accumulation is not required for the development of this aspect of the galactosemic phenotype [91]. Disturbances to the UDP-sugar pools and subsequent disruption of the glycosylation of neuronal proteins may be important in this model [92,93]. UDP-glucose pyrophosphorylase (UGP; EC 2.7.7.9) has been suggested as a possible drug target based on these studies [93]. Currently, no drugs are in clinical use which target this enzyme.

In rats fed with excess galactose, high levels of sodium ions were observed in the endoneurial fluid. This was proposed to result in osmotic withdrawal of water from the neurons [94]. The build-up of sodium ions can be reversed by the aldose reductase inhibitor, Ponalrestat (Statil, ICI 128436; CAS: 72702-95-5; Figure 4) [95]. This protects the Schwann cells and reduces the osmotic uptake of water into neurons [96]. To date, no causal link has been formally made between the build-up of sodium ions and the damage to nerves in galactosemia (or galactose toxicity). Therefore, it is uncertain if reversing this build-up using aldose reductase inhibitors would be therapeutically beneficial for galactosemia patients. However, aldose reductase inhibitors have been suggested as a treatment for galactosemic cataracts [97,98]. If this was widely adopted, it might also have beneficial effects on the nervous system.

6. Treatment for premature ovarian insufficiency in galactosemia

The biochemical origins of ovarian failure of galactosemic women are uncertain [99]. It was thought that failure of correct glycosylation of follicle stimulating hormone (FSH) may play a role in ovarian failure [100]. However, more recent studies have shown no evidence of alterations to FSH in some patients and no link between aberrant glycosylation of this hormone and fertility loss in galactosemic patients [101-103]. Studies using a rat model of galactosemia, which recapitulates the loss of fertility phenotype seen in humans, suggest that disruption of some signalling pathways may also be important. Of particular interest, the phosphoinositide 3-kinase (PI3K; EC 2.7.1.137)/Akt (protein kinase B; EC 2.7.11.1) growth signalling pathway is down-regulated in a mouse model of type I galactosemia [104]. These effects can be reversed by salubrinal (CAS: 405060-95-9; Figure 4), an inhibitor of the eukaryotic initiation factor 2α (eIF2α) phosphatase (EC 3.1.3.16), which alleviates endoplasmic reticulum stress and reduces the unfolded protein response [105,106]. This pharmacological intervention protects the mouse model from primordial follicle loss and increases fertility [107]. Salubrinal is not used clinically as an eIF2α phosphatase inhibitor. Another

compound, guanabenz (CAS: 5051-62-7; Figure 4), inhibits eIF2α phosphatase and is already in clinical use to treat hypertension [108]. It is not yet known if this compound has a similar effect on PI3K/Akt signalling, endoplasmic reticulum stress and fertility in galactosemic mammals. If it did have similar effects, it should be considered as a possible treatment for premature ovarian insufficiency in galactosemic patients. Given its role in modulating signalling and cellular stress, and its ability to cross the blood-brain barrier, it is possible that it would have wider, beneficial effects in other tissues [109,110]. As such it might represent a more general treatment for type I galactosemia.

A recent study has demonstrated a protective effect of the steroid dehydroepiandrosterone (DHEA; CAS: 53-43-0; Figure 4) on rats fed excess galactose [111]. Untreated rats have lower fertility than those fed DHEA in addition to galactose. This protection was associated with increased expression of Ki67 and reduced amounts of cleaved caspase 3 [111]. This, presumably, reduces apoptosis. DHEA occurs naturally in humans as a precursor in sex hormone biosynthesis [112]. It is used pharmacologically as a component of hormonal treatments for menopause [113]. There is some uncertainty about the long term safety of DHEA use, but its widespread use as a medicine and a health supplement suggest that it could be considered for the treatment of premature ovarian insufficiency in female galactosemia patients [114].

6. Expert opinion

The current treatment for galactosemia, dietary restriction of galactose, is inadequate and widely recognised as such. Exciting possibilities for treatment are in the pipeline: gene therapy, gene editing, enzyme replacement therapy and small molecule therapies. However, the time to develop these concepts and translate them into therapies is likely to be many years, perhaps more than a decade. Repurposing existing treatments offers the potential to improve therapy on a much shorter timescale. Existing therapies for other diseases have generally been tested for toxicity and side-

effects. Drugs which are in use for other diseases have already been formulated for delivery to patients. These treatments are likely to be most effective when used alongside a galactose restricted diet. Furthermore, they are unlikely to be as effective as bespoke treatments for galactosemia. Therefore, efforts to develop these should continue.

The following recommendations are made:

1. Patients with galactosemia should be advised to follow a diet high in antioxidants while not compromising the galactose restriction (i.e. food should be selected with high levels of antioxidant, but no galactose). Ascorbate, α-tocopherol, resveratrol and anthocyanins may be particularly useful compounds to prioritise.
2. Purple sweet potato colour, other plant-based antioxidants shown to mitigate galactose toxicity, idebenone and metformin should be tested in cellular and animal models of galactosemia. Any substances which show promise in these models should be considered for clinical trials.
3. Clinical trials on the use of resveratrol alongside dietary restriction of galactose should be considered.
4. Clinical trials on the use of MnTE-2-PyP^{5+} alongside dietary restriction of galactose should be considered.
5. Further research to understand the molecular causes of free radical generation in galactosemia is required. This would help clarify the antioxidants most likely to work and which should be prioritised for testing.
6. Clinical trials on the use of phosphate supplementation alongside dietary restriction of galactose should be considered.
7. In the planning of diets for galactosemia patients, the phosphate content should be considered.

8. Further research is required to understand the biochemical and physiological causes of movement disorders in galactosemic patients. This may facilitate the repurposing of drugs used in other diseases which result in movement disorders.
9. Aldose reductase inhibitors may have benefits beyond the prevention of reversal of cataracts. These should be investigated further with a particular emphasis on the consequences for nerve cells and the control of movement.
10. Further research to understand the molecular pathology of premature ovarian insufficiency in galactosemia is required.
11. Guanabenz should be tested to see if it has similar effects to salubrinal. If it does increase fertility in the mouse model, it should be considered for human trials. Dehydroepiandrosterone should also be considered for human trials.
12. Current research on more specific treatments for galactosemia should continue. While the recommendations above may improve the outcomes for galactosemia patients, they are still likely to be unsatisfactory.

These suggestions have the potential to deliver incremental benefits for patients with galactosemia. Some may continue to be useful once more specific therapies are available. Some may also be applicable to other inherited metabolic diseases which currently lack adequate therapies. In particular, if antioxidant therapy proved useful in galactosemia, it is likely to be valuable in other conditions in which free radical accumulation is a factor. Therefore, testing these ideas in galactosemia, may also result in improved therapies for other inherited metabolic diseases.

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Conflict of Interest

The author has no conflicts of interest concerning this work.

Figure legends

Figure 1: The metabolic conversion of D-galactose into the glycolytic intermediate glucose 6-phosphate. Galactose exists in solution in equilibrium between the α- and β-anomers. Their interconversion is catalysed by galactose mutarotase (GALM). Only the α-anomer enters the Leloir pathway, which begins with the phosphorylation of galactose, catalysed by galactokinase (GALK1). This is converted to glucose 1-phosphate (normally regarded as the product of the Leloir pathway) by the action of galactose 1-phosphate uridylyltransferase (GALT). UDP-galalctose is recycled to UDP-glucose by the action of UDP-galactose 4'-epimerase (GALE). To enter glycolysis, glucose 1-phosphate must be isomerised to glucose 6-phosphate. This reaction is catalysed by phosphoglucomutase (PGM). The types of galactosemia associated with the enzymes are shown in *italics* under the enzyme name.

Figure 2: Dietary antioxidants with potential for treating galactosemia

Figure 3: Pharmaceutical antioxidants with potential for treating galactosemia

Figure 4: Drugs which might be repurposed for (a) the treatment of movement disorders and (b) the treatment of premature ovarian insufficiency in galactosemia.

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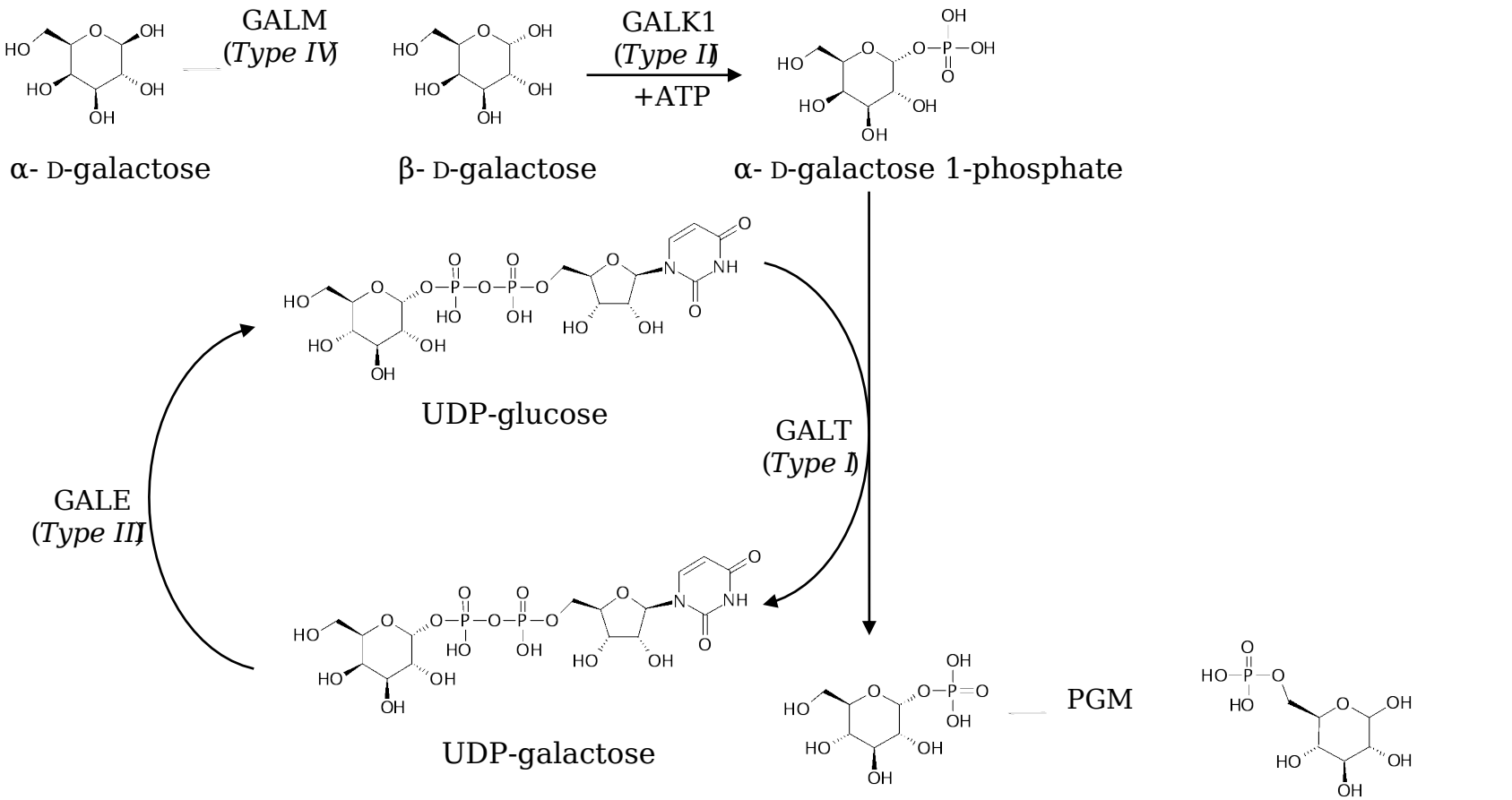
GALM
(Type IV)
GALK1
(Type II)
+ATP
α- D-galactose
β- D-galactose
α- D-galactose 1-phosphate
UDP-glucose
GALT
(Type I)
GALE
(Type III)
UDP-galactose
PGM
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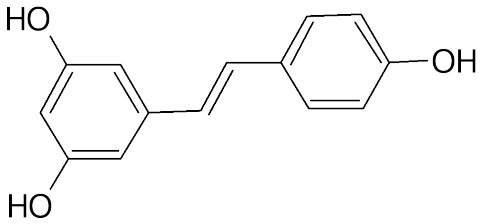
D-glucose 6-phosphate



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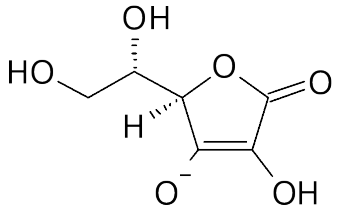

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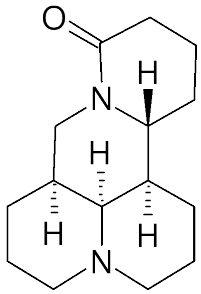

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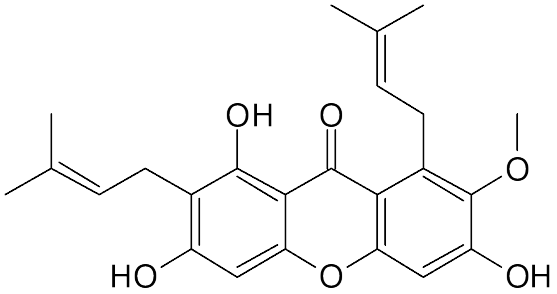
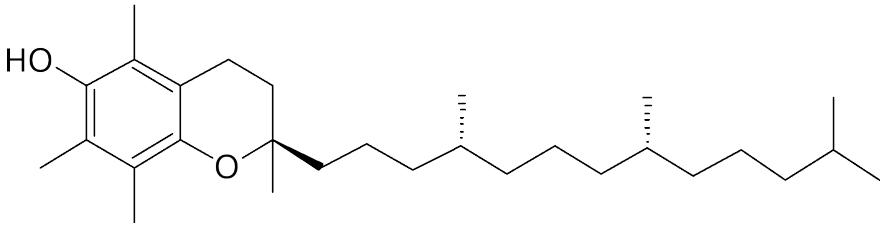


α-mangostin



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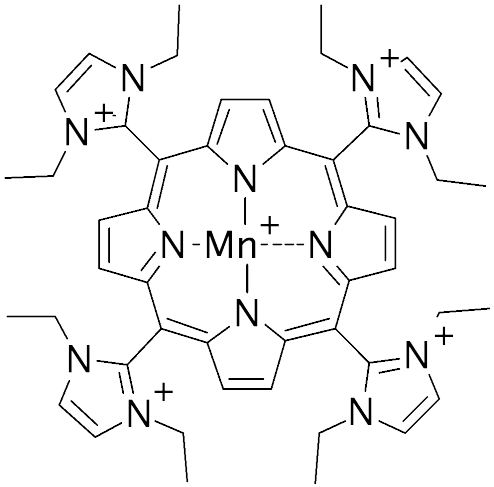
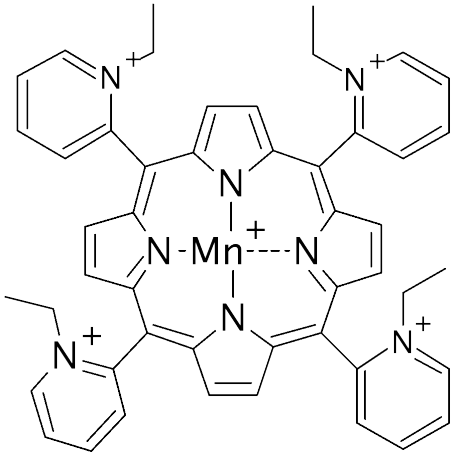


MnTDE-2-ImP^{5+}; AEOL-10150



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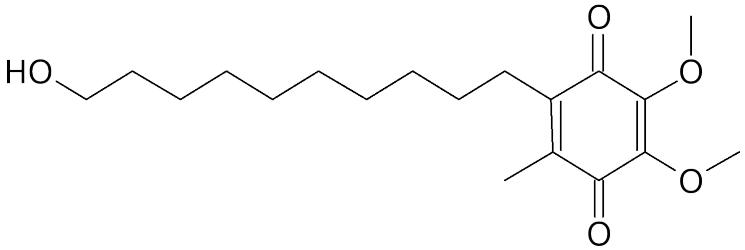

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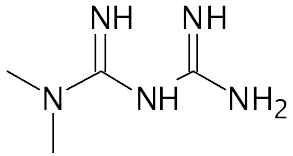
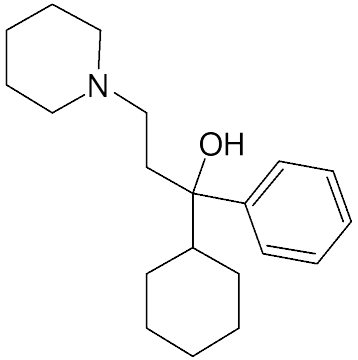


Metformin

(a)



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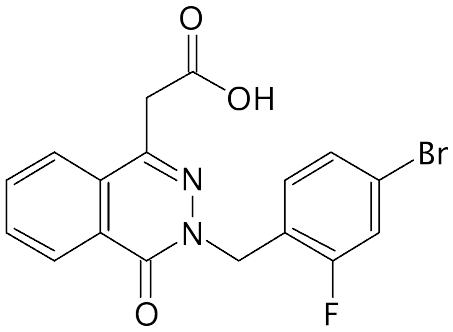
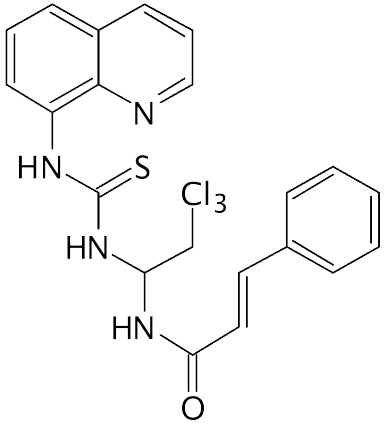


Ponalrestat

(b)



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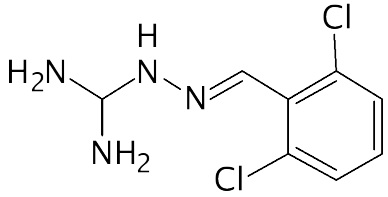

Guanabenz