

**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
- eIF2 $\alpha$  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  $\beta$ -D-galactose. In aqueous solution, the two anomers of D-galactose ( $\alpha$ -D-galactose and  $\beta$ -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  $\alpha$ -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  $\alpha$ -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  $\alpha$ -D-galactose 1-phosphate participates in an exchange reaction with UDP-glucose, generating  $\alpha$ -D-glucose 1-phosphate and UDP-galactose. This reaction is catalysed by galactose 1-phosphate uridylyltransferase (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  $\alpha$ -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:  $\alpha$ -D-glucose 1-phosphate is isomerised to D-glucose 6-

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3 phosphate in a reaction catalysed by phosphoglucomutase (PGM; EC 5.4.2.2) [19]. To date, no form  
4  
5 of galactosemia has been associated with this enzyme. However, congenital disorder of  
6  
7 glycosylation, type It (OMIM #614921) is associated with PGM1 deficiency. The glycosylation  
8  
9 disorders have some similarity with those seen in galactosemia types I and III [20].  
10  
11

12 The symptoms of galactosemia are highly variable [21-25]. The most severe forms result in  
13  
14 significant cognitive and physical disability in childhood and can result in death of the infant if  
15  
16 untreated. The mildest forms result in perturbations of blood chemistry which are not currently  
17  
18 associated with any adverse effects on the patient. Almost all forms, except the very mildest, result  
19  
20 in childhood onset cataracts. These result from the build-up of galactose in the lens. This is  
21  
22 converted to the sugar alcohol galactitol (dulcitol) by the action of aldose reductase (EC 1.1.1.21).  
23  
24

25 Unlike galactose, galactitol cannot be transported across the cell membrane and thus accumulates in  
26  
27 the lens cells, upsetting the osmotic balance of these cells [26]. The most severe symptoms are  
28  
29 associated with type I and some instances of type III galactosemia. Type III galactosemia probably  
30  
31 has the widest phenotypic range [27]. In addition to severely disabling and life-threatening  
32  
33 outcomes, it can also result in very mild symptoms which cause little or no harm. Types II and IV  
34  
35 have similar symptoms. Typically patients with these types of galactosemia have early onset  
36  
37 cataracts, normally in early childhood [8,28,29]. The severity of the symptoms depend on the exact  
38  
39 mutation(s) present in the patient along with the patient's environment. In this context, the  
40  
41 environment includes the health care available to the patient: early identification of the disease and  
42  
43 intervention can slow or prevent the development of some symptoms.  
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49 The only recognised treatment for all types of galactosemia is the exclusion, or reduction, of  
50  
51 galactose from the diet [21]. There is currently considerable debate about the necessity for  
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53 strictness in the dietary regime, particularly in adult patients [30]. Despite the potentially  
54  
55 devastating symptoms of type I galactosemia, a number of patients have recently been reported to  
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3 maintain levels of cognitive function sufficient to enable them to graduate with university degrees  
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5 [31].  
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8 The molecular and cellular pathology of galactosemia is not well understood, except for the  
9  
10 development of cataracts (see above). This lack of understanding hinders attempts to develop more  
11  
12 effective treatments. In affected individuals, the liver, brain and ovaries are often the most affected  
13  
14 organs [21,32]. Movement disorders have been reported in some patients [33]. The liver is the  
15  
16 main site for the Leloir pathway and it is believed that the accumulation of galactose 1-phosphate is  
17  
18 toxic to cells. The mechanism of this toxicity has not been definitively determined. It should also be  
19  
20 noted that galactose itself is toxic at higher concentrations (>5 mM) and several studies have  
21  
22 demonstrated that the administration of high levels of galactose to healthy animals results in similar  
23  
24 pathology to galactosemia [34,35]. Disturbances in glycoprotein and glycolipid synthesis may partly  
25  
26 explain the effects on the brain and ovaries [36,37]. Increased cellular free radical load is also  
27  
28 associated with the galactosemic phenotype [38]. This is likely to represent a secondary  
29  
30 consequence of metabolic disturbances which then causes further, non-specific damage to cellular  
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32 components.  
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38 While the dietary restriction of galactose is helpful in most patients, it often only slows and reduces  
39  
40 the severity of the symptoms. Even with a galactose restricted diet many patients suffer physical  
41  
42 and mental disability [39]. A number of other therapies have been proposed [40]. These include the  
43  
44 inhibition of GALK1. While this would, presumably, cause similar symptoms to type II galactosemia,  
45  
46 it would prevent the build-up of galactose 1-phosphate which is thought to be responsible for some  
47  
48 of the more severe pathology in types I and III [29,41]. A number of effective and selective inhibitors  
49  
50 have been identified, but none are in clinical use yet [41]. Enzyme replacement therapy works by  
51  
52 delivering pure, recombinant enzyme to the affected tissues. In theory, this could be applied in  
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54 galactosemia. However, it may be necessary to overcome delivery problems to the brain where the  
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56 blood-brain barrier typically prevents the passage of larger molecules like proteins. Gene therapy is  
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3 also possible in theory, but again there may be a need to deliver larger hydrophilic molecules across  
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5 the blood brain barrier in order to restore activity in this organ. Since many of the disease-  
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7 associated variants of GALT, GALK1, GALE and GALM are less thermally stable than the wild-type  
8  
9 protein, small molecule pharmacological chaperones could be deployed to assist their folding and  
10  
11 increase enzymatic activity [8,42-44]. To date, no suitable molecules have been reported, although a  
12  
13 promising binding site in GALT has been identified by *in silico* methods [40,42]. All these approaches  
14  
15 have considerable promise. Most would all wholly or partly restore the activity of the affected  
16  
17 enzyme and, presumably, alleviate the majority of the symptoms. However, they are all many years  
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19 from being implemented in patients. Considerable basic science work is required on all these  
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21 approaches before the lengthy process of clinical trials and gaining regulatory approval could begin.  
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23 This review focuses on existing drugs (and drug-like molecules) which might be redeployed to treat  
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25 galactosemia.  
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## 34 **2. Antioxidants - dietary**

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36 Since oxidative stress has been identified as a common occurrence in cells from galactosemic patients  
37  
38 and in animal models of galactosemia, it has been suggested that reducing this stress may have  
39  
40 benefit to patients [38,45]. This proposition is also supported by animal studies on galactose  
41  
42 toxicity. Injection of galactose into rat cerebellums caused an increase in reactive oxygen species,  
43  
44 damage to proteins and reduction in cognitive function. These effects were suppressed by the co-  
45  
46 administration of the antioxidants ascorbic acid (vitamin C; CAS: 50-81-7; Figure 2) or  $\alpha$ -tocopherol  
47  
48 (vitamin E; CAS: 59-02-9; Figure 2) [35]. Ascorbate and the plant-derived xanthanoid  $\alpha$ -mangostin  
49  
50 (CAS: 6147-11-1; Figure 2) protected against oxidative stress and reduced the severity of the  
51  
52 galactosemia-like phenotype in a *Drosophila melanogaster* model of the disease [38]. A number  
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54 plant extracts and plant-derived compounds have been shown to have similar effects in animals  
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56 exposed to excess galactose. Particularly impressive results have been obtained with purple sweet  
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3 potato colour, an extract containing anthocyanins and phenolic compounds [46-50]. In parallel to  
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5 oxidative stress, high galactose concentrations induce cellular senescence, a condition in which cells  
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7 permanently cease to divide without undergoing any form of cell death [51]. Some antioxidant  
8  
9 compounds, for example the plant alkaloid matrine (CAS: 519-02-8; Figure 2), inhibit the induction  
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11 of senescence in animal models of galactose toxicity [52].  
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15 The ideal dietary antioxidant to use in galactosemia would be readily available, safe to use for  
16  
17 extended periods, cross the blood-brain barrier and would combine free radical quenching  
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19 properties with anti-senescent activity. Purple sweet potato extracts, along with drinks derived from  
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21 this vegetable are widely consumed in Japan with no significant ill-effects reported [53,54]. The  
22  
23 anthocyanins in the extract are known to be absorbed by mammals and to increase antioxidant  
24  
25 activity in the blood plasma [55]. There is also some evidence that it inhibits senescence [56]. The  
26  
27 combination of these two effects would make purple sweet potato colour potentially attractive as a  
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29 therapy for galactosemia [57].  
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33 Resveratrol (CAS: 501-36-0; Figure 2), a stilbenoid found in grapes and other fruits, also protects  
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35 against galactose toxicity, partly by reducing oxidative stress [58]. In addition to its antioxidant  
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37 activity, resveratrol has several protein targets. These include inhibition of NRH-quinone  
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39 oxidoreductase 2 (NQO2) and activation of the histone deacetylase sirtuin-1 (SIRT-1) [59,60]. It is  
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41 considered generally safe, with minimal side-effects at doses up to several hundred milligrams per  
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43 day [61]. There are some concerns that doses in the grams per day range may be harmful and, as  
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45 will all drugs, interactions with other drugs and inhibition of the cytochrome P450 system should be  
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47 considered [61-63]. Resveratrol also demonstrates impressive anti-senescent effects. Not only does  
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49 it inhibit senescence, but can also reverse the process through modulation of RNA splicing. This  
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51 enables cells to exit from senescence, increase telomere length and resume proliferation [64]. It is  
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53 known to cross the blood-brain barrier and has been proposed as a treatment for some neurological  
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55 diseases [65,66]. These combined properties make resveratrol an attractive proposition for use in  
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3 galactosemia patients. However, other dietary antioxidants may also be effective; further testing  
4 may help determine which are the most promising for clinical trials. The recent development of a  
5 credible mouse model for type I galactosemia could help with this, and other evaluations of possible  
6 treatments [67]. Even before such results are available, it should be noted that high antioxidant  
7 diets are generally considered to deliver a range of health benefits [68]. Therefore, there would be  
8 little risk and some potential benefit in recommending such diets to galactosemia patients.  
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### 20 **3. Antioxidants – pharmaceutical**

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

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3 Antioxidants are used in other genetic diseases. Idebenone (CAS: 58186-27-9; Figure 3), is a  
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5 coenzyme Q<sub>10</sub> (CoQ; ubiquinone; CAS: 303-98-0) mimic developed by the Takeda Pharmaceutical  
6  
7 Company. It is used in the treatment of  
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#### 10 11 12 13 **4. Phosphate supplementation** 14

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16 Types I and III galactosemia result in a cellular build-up of galactose 1-phosphate. This molecule is  
17  
18 considered to be toxic to cells, although no molecular target(s) have been conclusively identified.

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20 Another detrimental effect of the accumulation of this compound is the reduction in the amount of  
21  
22 phosphate available to other metabolic processes. Phosphate is essential for energy metabolism  
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24 involving ATP, the synthesis of nucleic acids and phospholipids, and the control of protein activity by  
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26 phosphorylation. Disruption of any of these processes is likely to be detrimental to the cell and the  
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28 organism.  
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32 Deletion of the gene encoding GALT in budding yeast *Saccharomyces cerevisiae* (*GAL7*) resulted in  
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34 depletion in cellular inorganic phosphate levels [84]. Similar effects have been observed in the  
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36 serum of patients with galactosemia and hereditary fructose intolerance (OMIM #229600), another  
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38 disease which results in the accumulation of a sugar phosphate [85]. In the yeast model, this  
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40 phosphate depletion resulted in altered glycogen metabolism, presumably because phosphate ions  
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42 are required for the enzymatic breaking of  $\alpha(1\rightarrow4)$  glycosidic bonds in this polysaccharide. Reversal  
43  
44 of phosphate depletion either by deletion of the galactokinase gene (*GAL1*) or supplementation of  
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46 the media with phosphate ions prevented the reduction of cellular phosphate levels and restored  
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48 normal glycogen metabolism [84]. This suggests that phosphate supplementation in galactosemia  
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50 patients would be worth investigating.  
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55 Phosphate supplementation is already used in a variety of conditions, including the treatment of  
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57 some alcoholics and patients undergoing renal dialysis or kidney transplants, diabetic ketoacidosis,  
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3 burns and sepsis [86]. It is generally considered safe, although care needs to be taken if some other  
4 medicines are being used at the same time [87,88]. Pharmaceutical preparations already exist in  
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6 both dissolvable tablets and injectable forms. Therefore the investigation of phosphate  
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8 supplementation as a possible therapy for galactosemia may prove fruitful and is unlikely to present  
9  
10 significant risks to patients. It should also be noted that milk (and milk products) are good sources of  
11  
12 dietary phosphate [89]. These are, of course, eliminated or substantially reduced in the  
13  
14 galactosemic diet. Therefore, it may be the case that some patients are on reduced phosphate  
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16 intake diets which would further reduce the availability of phosphate in their cells.  
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## 25 **5. Treatment of movement disorders in galactosemia**

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27 Movement disorders occur in some patients with type I galactosemia [33]. Dystonia (sustained,  
28 uncontrolled muscle contractions is the most commonly observed symptom and weaknesses which  
29 results in reduced dexterity and balance is also seen [33,90]. Treatment is not always given,  
30 although patients are often supported by physiotherapy and occupational therapy. One patient has  
31 been reported to have been treated with trihexyphenidyl (CAS: 144-11-6; Figure 4) and botulinum  
32 toxin in addition to a lycra suit [33]. Trihexyphenidyl is used in the treatment of Parkinson's disease  
33 and other conditions which result in involuntary movements and botulinum toxin is used as a muscle  
34 relaxant in a variety of diseases. Wider consideration of the use of existing drugs to treat dystonia  
35 and ataxia may be worth considering for galactosemia patients.  
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48 The molecular causes of these movement disorders remain unknown. Work on the *D. melanogaster*  
49 model suggests that galactose 1-phosphate accumulation is not required for the development of this  
50 aspect of the galactosemic phenotype [91]. Disturbances to the UDP-sugar pools and subsequent  
51 disruption of the glycosylation of neuronal proteins may be important in this model [92,93]. UDP-  
52 glucose pyrophosphorylase (UGP; EC 2.7.7.9) has been suggested as a possible drug target based on  
53 these studies [93]. Currently, no drugs are in clinical use which target this enzyme.  
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3 In rats fed with excess galactose, high levels of sodium ions were observed in the endoneurial fluid.  
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5 This was proposed to result in osmotic withdrawal of water from the neurons [94]. The build-up of  
6  
7 sodium ions can be reversed by the aldose reductase inhibitor, Ponalrestat (Statil, ICI 128436; CAS:  
8  
9 72702-95-5; Figure 4) [95]. This protects the Schwann cells and reduces the osmotic uptake of water  
10  
11 into neurons [96]. To date, no causal link has been formally made between the build-up of sodium  
12  
13 ions and the damage to nerves in galactosemia (or galactose toxicity). Therefore, it is uncertain if  
14  
15 reversing this build-up using aldose reductase inhibitors would be therapeutically beneficial for  
16  
17 galactosemia patients. However, aldose reductase inhibitors have been suggested as a treatment  
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19 for galactosemic cataracts [97,98]. If this was widely adopted, it might also have beneficial effects  
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21 on the nervous system.  
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## 29 **6. Treatment for premature ovarian insufficiency in galactosemia**

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32 The biochemical origins of ovarian failure of galactosemic women are uncertain [99]. It was thought  
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34 that failure of correct glycosylation of follicle stimulating hormone (FSH) may play a role in ovarian  
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36 failure [100]. However, more recent studies have shown no evidence of alterations to FSH in some  
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38 patients and no link between aberrant glycosylation of this hormone and fertility loss in  
39  
40 galactosemic patients [101-103]. Studies using a rat model of galactosemia, which recapitulates the  
41  
42 loss of fertility phenotype seen in humans, suggest that disruption of some signalling pathways may  
43  
44 also be important. Of particular interest, the phosphoinositide 3-kinase (PI3K; EC 2.7.1.137)/Akt  
45  
46 (protein kinase B; EC 2.7.11.1) growth signalling pathway is down-regulated in a mouse model of  
47  
48 type I galactosemia [104]. These effects can be reversed by salubrinal (CAS: 405060-95-9; Figure 4),  
49  
50 an inhibitor of the eukaryotic initiation factor 2 $\alpha$  (eIF2 $\alpha$ ) phosphatase (EC 3.1.3.16), which alleviates  
51  
52 endoplasmic reticulum stress and reduces the unfolded protein response [105,106]. This  
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54 pharmacological intervention protects the mouse model from primordial follicle loss and increases  
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56 fertility [107]. Salubrinal is not used clinically as an eIF2 $\alpha$  phosphatase inhibitor. Another  
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3 compound, guanabenz (CAS: 5051-62-7; Figure 4), inhibits eIF2 $\alpha$  phosphatase and is already in  
4 clinical use to treat hypertension [108]. It is not yet known if this compound has a similar effect on  
5  
6 PI3K/Akt signalling, endoplasmic reticulum stress and fertility in galactosemic mammals. If it did  
7  
8 have similar effects, it should be considered as a possible treatment for premature ovarian  
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10 insufficiency in galactosemic patients. Given its role in modulating signalling and cellular stress, and  
11  
12 its ability to cross the blood-brain barrier, it is possible that it would have wider, beneficial effects in  
13  
14 other tissues [109,110]. As such it might represent a more general treatment for type I  
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16 galactosemia.  
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21 A recent study has demonstrated a protective effect of the steroid dehydroepiandrosterone (DHEA;  
22 CAS: 53-43-0; Figure 4) on rats fed excess galactose [111]. Untreated rats have lower fertility than  
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24 those fed DHEA in addition to galactose. This protection was associated with increased expression  
25  
26 of Ki67 and reduced amounts of cleaved caspase 3 [111]. This, presumably, reduces apoptosis.  
27  
28 DHEA occurs naturally in humans as a precursor in sex hormone biosynthesis [112]. It is used  
29  
30 pharmacologically as a component of hormonal treatments for menopause [113]. There is some  
31  
32 uncertainty about the long term safety of DHEA use, but its widespread use as a medicine and a  
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34 health supplement suggest that it could be considered for the treatment of premature ovarian  
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36 insufficiency in female galactosemia patients [114].  
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## 46 **6. Expert opinion**

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48 The current treatment for galactosemia, dietary restriction of galactose, is inadequate and widely  
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50 recognised as such. Exciting possibilities for treatment are in the pipeline: gene therapy, gene  
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52 editing, enzyme replacement therapy and small molecule therapies. However, the time to develop  
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54 these concepts and translate them into therapies is likely to be many years, perhaps more than a  
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56 decade. Repurposing existing treatments offers the potential to improve therapy on a much shorter  
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58 timescale. Existing therapies for other diseases have generally been tested for toxicity and side-  
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3 effects. Drugs which are in use for other diseases have already been formulated for delivery to  
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5 patients. These treatments are likely to be most effective when used alongside a galactose  
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7 restricted diet. Furthermore, they are unlikely to be as effective as bespoke treatments for  
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9 galactosemia. Therefore, efforts to develop these should continue.  
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13 The following recommendations are made:  
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- 15  
16 1. Patients with galactosemia should be advised to follow a diet high in antioxidants while not  
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18 compromising the galactose restriction (i.e. food should be selected with high levels of  
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20 antioxidant, but no galactose). Ascorbate,  $\alpha$ -tocopherol, resveratrol and anthocyanins may  
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22 be particularly useful compounds to prioritise.  
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- 24  
25 2. Purple sweet potato colour, other plant-based antioxidants shown to mitigate galactose  
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27 toxicity, idebenone and metformin should be tested in cellular and animal models of  
28  
29 galactosemia. Any substances which show promise in these models should be considered  
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31 for clinical trials.  
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- 33  
34 3. Clinical trials on the use of resveratrol alongside dietary restriction of galactose should be  
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36 considered.  
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- 38  
39 4. Clinical trials on the use of MnTE-2-PyP<sup>5+</sup> alongside dietary restriction of galactose should be  
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41 considered.  
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44 5. Further research to understand the molecular causes of free radical generation in  
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46 galactosemia is required. This would help clarify the antioxidants most likely to work and  
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48 which should be prioritised for testing.  
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- 50  
51 6. Clinical trials on the use of phosphate supplementation alongside dietary restriction of  
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53 galactose should be considered.  
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56 7. In the planning of diets for galactosemia patients, the phosphate content should be  
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58 considered.  
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- 3 8. Further research is required to understand the biochemical and physiological causes of
- 4 movement disorders in galactosemic patients. This may facilitate the repurposing of drugs
- 5 used in other diseases which result in movement disorders.
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- 10 9. Aldose reductase inhibitors may have benefits beyond the prevention of reversal of
- 11 cataracts. These should be investigated further with a particular emphasis on the
- 12 consequences for nerve cells and the control of movement.
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- 16 10. Further research to understand the molecular pathology of premature ovarian insufficiency
- 17 in galactosemia is required.
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- 21 11. Guanabenz should be tested to see if it has similar effects to salubrinal. If it does increase
- 22 fertility in the mouse model, it should be considered for human trials.
- 23
- 24 Dehydroepiandrosterone should also be considered for human trials.
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- 28 12. Current research on more specific treatments for galactosemia should continue. While the
- 29 recommendations above may improve the outcomes for galactosemia patients, they are still
- 30 likely to be unsatisfactory.
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35 These suggestions have the potential to deliver incremental benefits for patients with galactosemia.

36 Some may continue to be useful once more specific therapies are available. Some may also be

37 applicable to other inherited metabolic diseases which currently lack adequate therapies. In

38 particular, if antioxidant therapy proved useful in galactosemia, it is likely to be valuable in other

39 conditions in which free radical accumulation is a factor. Therefore, testing these ideas in

40 galactosemia, may also result in improved therapies for other inherited metabolic diseases.

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metabolising enzymes.

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6 **Conflict of Interest**  
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9 The author has no conflicts of interest concerning this work.  
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For Peer Review Only



## 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  $\alpha$ - and  $\beta$ -anomers. Their interconversion is catalysed by galactose mutarotase (GALM). Only the  $\alpha$ -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-galactose 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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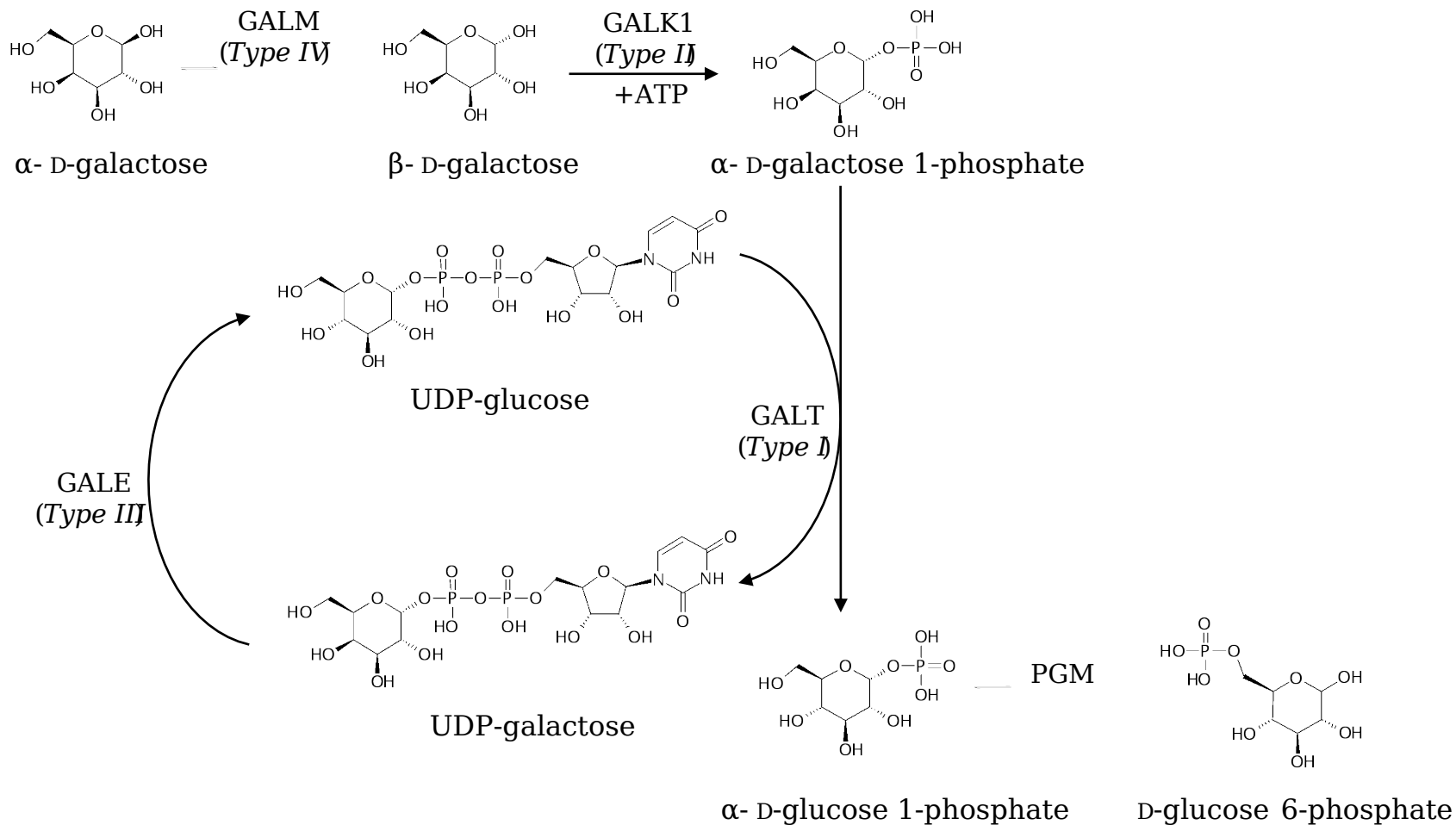
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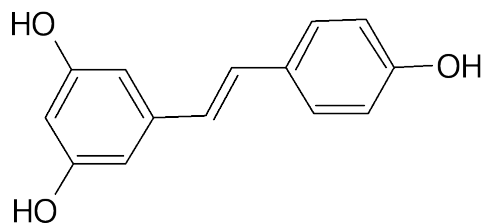
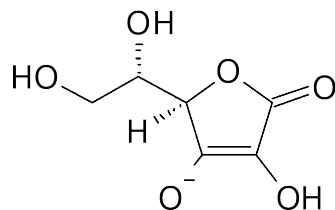
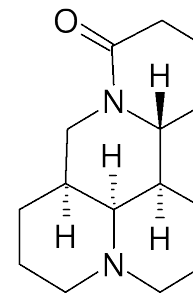
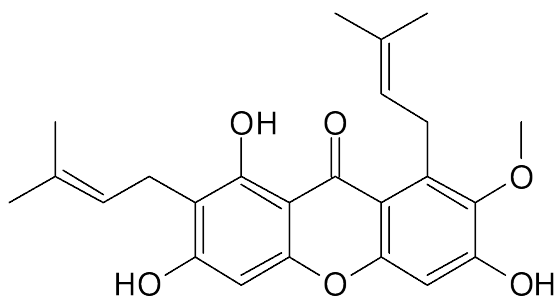
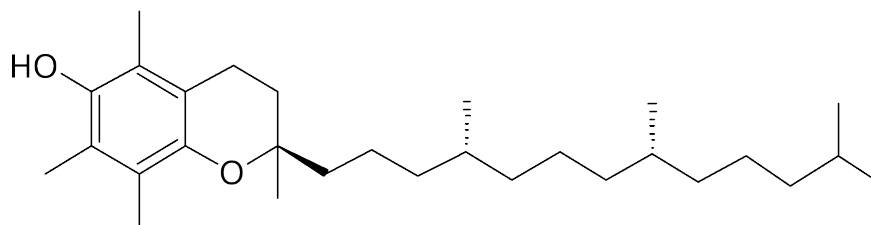
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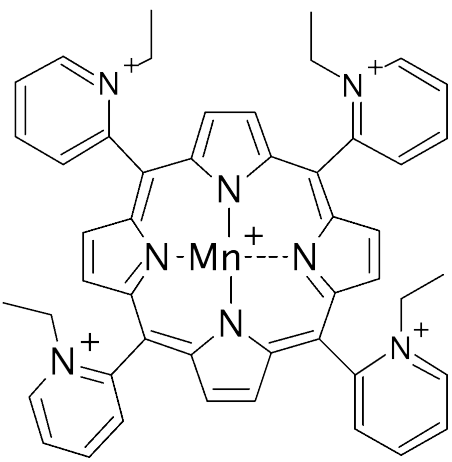
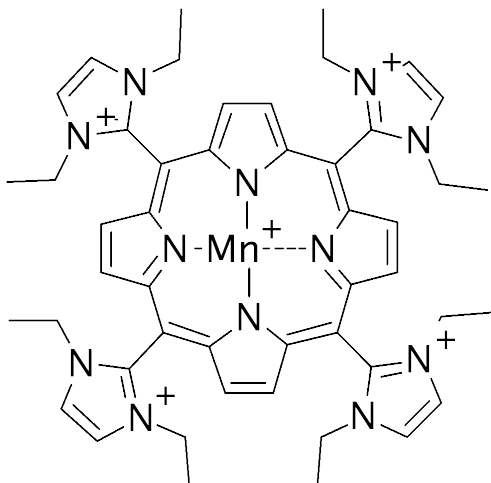
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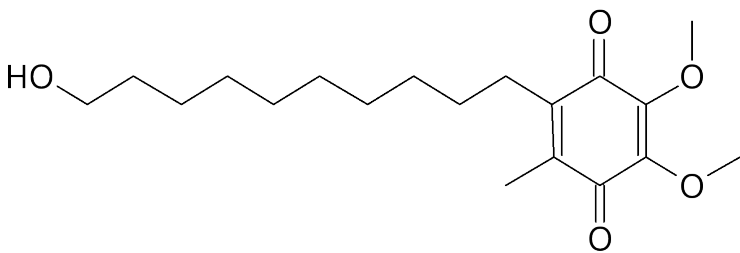
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**Resveratrol****L-Ascorbate****(+)-Matrine****α-mangostin****α-tocopherol**

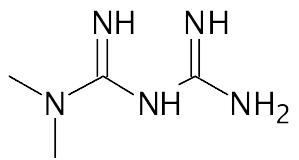
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**MnTDE-2-ImP<sup>+</sup>; AEOL-10113; AEOL-10113**

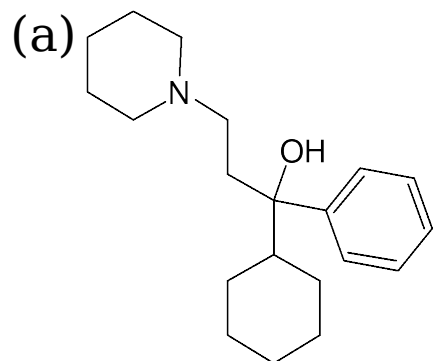


**Idabenone**

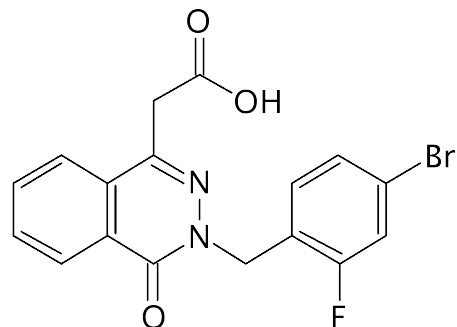


**Metformin**

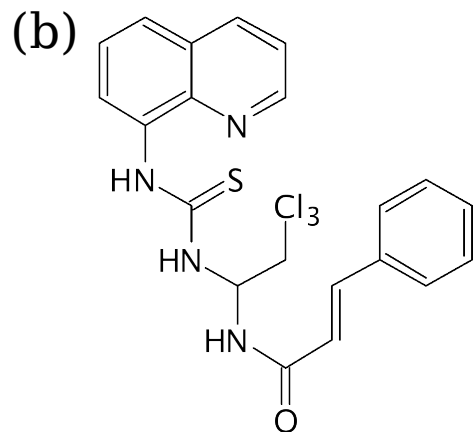




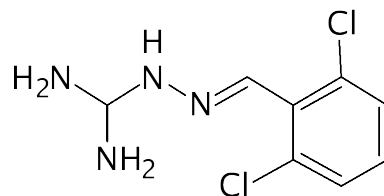
Trihexyphenidyl



Ponalrestat



Salubrinal



Guanabenz