

# **The Effects of Liquorice on Blood Pressure**

**A Study on the Hypertension-Inducing Mechanism of  
Glycyrrhizin**

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## Abstract

Liquorice is made of a plant extract with a long history in traditional Chinese and Western medicine in the treatment of various diseases. Yet cases covered in the media<sup>1,2</sup> and more recent studies have proved liquorice to be relatively ambiguous, as more adverse health effects have been revealed.<sup>3,4</sup> The aim of this research is to determine the metabolic pathways through which glycyrrhizin in liquorice-derived compounds causes hypertension. Due to ethical issues as well as limitations on the scope of a possible experiment, the research was limited to a literature-based dissertation. Dose-effect relationships have been discussed, and a short inquiry was conducted to estimate the magnitude of liquorice confectionery consumption in Finland.

Through the investigation of various scientific journals as well as literature on mammalian physiology, the *Glycyrrhiza glabra* plant from which liquorice extract is obtained was first studied to determine the main bioactive component, glycyrrhizin. The various enzymes inhibited by glycyrrhetic acid, a derivative of glycyrrhizin, and their relevant functions have been presented as to provide insight to their normal mechanisms. The renin-angiotensin-aldosterone system (RAAS) was reviewed within context, and the role and consequential effects of glycyrrhizin in mammalian metabolism were identified.

By inhibiting 11 $\beta$ -hydroxysteroid dehydrogenase (11 $\beta$ -OHSD)<sup>5</sup> glycyrrhetic acid induces an apparent hypermineralocorticoid effect. This will cause sodium retention, hypokalemia, increased water retention, expanded extracellular fluid volume and hypertension.<sup>6</sup> These symptoms act as negative feedback, reducing the production of renin in the kidneys. This ultimately causes the suppression of the whole RAAS due to the reduction in synthesis of aldosterone. The inhibitory effect of 11 $\beta$ -OHSD is reversible and the aforementioned symptoms will eventually disappear, but the subsequent effects of suppressing the RAAS may last for 1-2 months even after intake of glycyrrhizin has ceased.

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<sup>1</sup> BBC News, 2004

<sup>2</sup> Berliner Kurier textarchiv, 2004

<sup>3</sup> Davis & Morris, 1990

<sup>4</sup> Fenwick *et al.*, 1990

<sup>5</sup> Baker, 1994

<sup>6</sup> Stormer *et al.*, 1993

## Tiivistelmä

Lakritsi valmistetaan kasviuutteesta, jolla on pitkä historia niin perinteisessä kiinalaisessa kuin länsimaisessakin lääketieteessä useiden sairauksien hoidossa. Julkisuudessa esillä olleet tapaukset<sup>1,2</sup> sekä tuoreemmat tutkimukset ovat paljastaneet lakritsin vaikutusten olevan luultua monimutkaisempia haittavaikutusten tullessa esiin.<sup>3,4</sup> Tämän tutkielman tarkoitus on määrittää aineenvaihdunnalliset mekanismit, joiden välityksellä glykyrritsiini lakritsiuutetta sisältävissä aineissa kohottaa verenpainetta. Eettisistä syistä ja mahdollisen tutkimuksen rajallisuuden vuoksi tutkielmani on täysin kirjallisuuspohjainen. Annos-vaikutussuhteita käsitellään ja lakritsimakeisten kulutuksen määrää Suomessa arvioidaan tekemäni pienen teollisuuskyselyn avulla.

Tieteellisten julkaisujen sekä biokemiaa käsittelevien teosten avulla *Glycyrrhiza glabra* –kasvia, josta lakritsiuute saadaan, tutkitaan ja merkittävin bioaktiivinen ainesosa määritetään. Glykyrritsiinihapon estämät entsyymit sekä niiden toiminnat esitetään, jotta normaalit mekanismit olisi helppo ymmärtää. Reniini-angiotensiini-aldosteroni-järjestelmä (RAA-järjestelmä) esitellään asiayhteydessä, ja glykyrritsiinin rooli ja seurannaisvaikutukset nisäkkäiden aineenvaihdunnassa tunnistetaan.

Estämällä  $11\beta$ -hydroksisteroididehydrogenaasientsyymiä ( $11\beta$ -OHSD)<sup>5</sup> glykyrritsiinihappo aiheuttaa näennäisen mineralokortikoidiylijäämän. Tämä aiheuttaa natriumretentiota, hypokaleemiaa, lisääntynyttä nesterentiota ja solunulkoista nestemäärää sekä kohottaa verenpainetta.<sup>6</sup> Nämä oireet toimivat negatiivisena palautevaikutuksena vähentäen reniinin tuotantoa munuaisissa. Tästä aiheutuu koko RAA-järjestelmän tukahduttaminen, kun aldosteronin tuotanto vähenee.  $11\beta$ -OHSD:n estävä vaikutus ei ole peruuttamaton ja edellä mainitut oireet häviävät ajan kanssa, mutta RAA-järjestelmän häiriintyminen voi jatkua yhdestä kahteen kuukautta lakritsin syönnin lopettamisen jälkeen.

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<sup>1</sup> BBC News, 2004

<sup>2</sup> Berliner Kurier textarchiv, 2004

<sup>3</sup> Davis & Morris, 1990

<sup>4</sup> Fenwick *et al.*, 1990

<sup>5</sup> Baker, 1994

<sup>6</sup> Stormer *et al.*, 1993

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## 1 Introduction

In 2004 BBC News reported of a 56-year-old woman having 'overdosed' on liquorice sweets: she went into muscle failure and had to be admitted to the hospital. Doctors said she had been eating liquorice to relieve chronic constipation. After having her dangerously low potassium levels restored with an intravenous drip and tablets, "she was up and walking within four days" stated Dr Hussain of Pontrefact General Infirmary.<sup>1</sup>

Similarly, only two months earlier, a 48-year-old woman in Bonn Germany sought well known sweets company Haribo €6000 in compensation for heart problems caused by excessive consumption of liquorice. She claimed that Haribo had not properly labeled the packages, informing her that the quantities of liquorice she was consuming could cause high blood pressure. Her case was overruled.<sup>2</sup>

Liquorice is made of a plant extract with an incredibly colourful history due to the various effects it has on the metabolism of mammals. From Ancient Egypt to monastery gardens in England, praised by Pliny the Elder in *The Natural History* (1856) and still used broadly in traditional Chinese medicine, liquorice has left a distinguishable mark in history as an almost totipotent herbal remedy. Yet more recent studies and investigations have proved liquorice to be relatively ambiguous, as more adverse health effects have been revealed.<sup>3,4,5</sup>

The use of liquorice extract in medicine may have reduced, but it still remains popular in the sweets and tobacco industries. Especially in Scandinavia liquorice sweets are found everywhere, both alone and mixed with other confectionery such as chocolate. In Nordic countries it is common to make a special type of liquorice by mixing it with great amounts of ammonium chloride (NH<sub>4</sub>Cl): this is known as salty liquorice or salmiac. Both liquorice and salty liquorice are often used in chewing gums, normal and nicotine-containing, as well as a flavouring agent in spirits.

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<sup>1</sup> BBC News, 2004

<sup>2</sup> Berliner Kurier textarchiv, 2004

<sup>3</sup> Davis & Morris, 1990

<sup>4</sup> Fenwick *et al.*, 1990

<sup>5</sup> Leppänen, 2004

Being a great fan of liquorice sweets myself, the chance to deepen my understanding and investigate the effects liquorice extract has on mammals seemed like an interesting challenge, as well as a possibility to increase my consumption in the name of empirical experiences. In addition to encountering an excuse to continue enjoying these particular confectionery products without guilt, there was the risk of coming across motives for halting consumption; the amount and scope of investigations conducted on the topic was surprisingly exhaustive, the vast majority dating to the early 1990s and focusing on negative effects.

The aim of this research is to determine the metabolic pathways through which glycyrrhizin in liquorice-derived compounds causes hypertension. I wished to include an experimental study to see the possible hypertension-inducing effects, but due to ethical issues as well as limitations on the scope of a possible experiment, the reliability of the data obtained would have been questionable. Therefore, limiting this research to a literature-based dissertation prevailed. As various papers read during the investigation have taken into consideration the link between the strength of the effects and the amount of liquorice consumed, dose-effect relationships have been discussed. A short inquiry was also conducted to estimate the magnitude of liquorice confectionery consumption in Finland.

## 2 *Glycyrrhiza glabra*

Liquorice is extracted from the root of the plant *Glycyrrhiza glabra* L. (Fig. 1). *G. glabra* is a 30-100cm tall leguminous shrub belonging to the *Fabaceae* family. It has pinnate leaves, sub-terrestrial roots and purple to blue flowers that grow in a loose inflorescence. *G. glabra* grows mainly in sub-tropical regions and can be found growing both wild and under cultivation. It is a



**Figure 1:** *Glycyrrhiza glabra* as illustrated in Prof. Dr. Otto Wilhelm Thomé's *Flora von Deutschland, Österreich und der Schweiz*, 1885

perennial herb, and similarly to many other perennial plants it reproduces mainly through vegetative multiplication (i.e. root cuttings or division of the crown). The plants are harvested only after at least two years of growth by cutting the roots. Some root material is always left behind, so that from this the next generation of plants will grow and in turn be harvested after a few years.<sup>6</sup>

### 2.1 Varieties of *Glycyrrhiza glabra*

There are considered to be four varieties of *Glycyrrhiza glabra*. The one that is used mainly in Europe is *G. glabra* var. *typica* Reg. Et Herd., which is found in the Mediterranean and Caucasian regions and is also called Spanish or Italian liquorice. Other varieties include *G. glabra* var. *violacea* Boiss. (Persian or Turkish liquorice) and *G. glabra* var. *pallida* Boiss., which both grow wild in the regions of old Mesopotamia. Finally, *G. glabra* var. *glandulifera* Reg. Et Herd., which is also known as Russian liquorice, is found in Hungary, Southern Siberia, Turkestan and Afghanistan. It should also be noted that the liquorice extract used in Chinese medicine is obtained from a separate species known as *Glycyrrhiza uralensis* Fisch., or Chinese liquorice.<sup>7</sup>

### 2.2. Composition of the roots

Liquorice extract is obtained from the roots by grinding them, after which they are cooked in water, followed by clarification and evaporation<sup>8</sup>. The most important and main bioactive component of the root, glycyrrhizin<sup>9</sup> is a triterpene glycoside and makes up 5-24% of the root. The exact amount varies according to the species, conditions of cultivation, growth environment, among other factors.<sup>10</sup>

According to a research conducted in Japan, the amounts of glycyrrhizin were highest after three years of growth and after senescence of the leaves in the autumn. A direct relationship between the diameter of fresh roots and amount of glycyrrhizin was observed. From the results, Hayashi *et al.* (1998) concluded "*glycyrrhizin content increased during the senescence of the aerial parts as well as during the early stage of*

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<sup>6</sup> Fenwick *et al.*, 1990

<sup>7</sup> Fenwick *et al.*, 1990

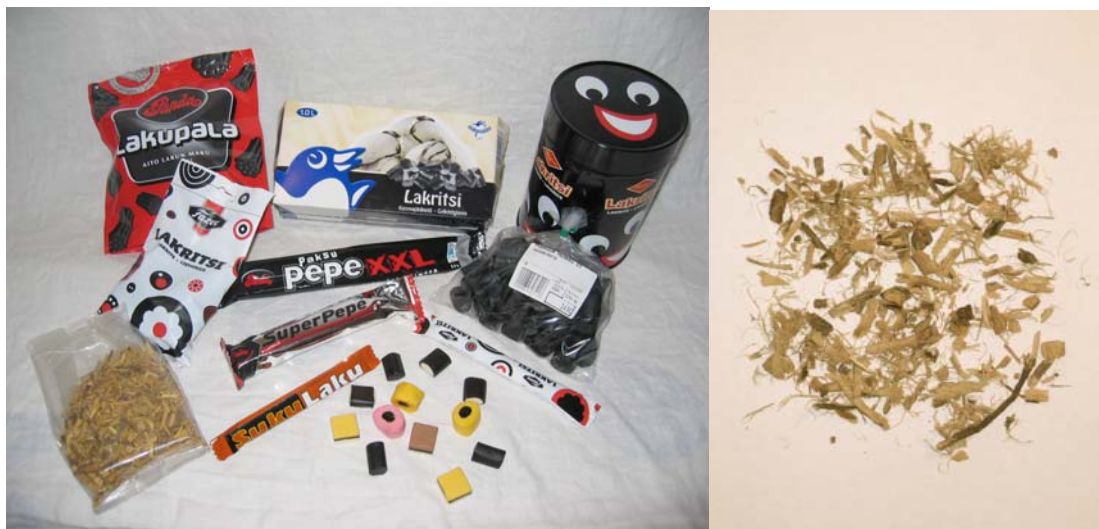
<sup>8</sup> Stormer *et al.*, 1993

<sup>9</sup> Glycyrrhizin has also been named glycyrrhizic/glycyrrhizinic acid. Its aglycone, glycyrrhetic acid, is also known by the name glycyrrhethinic acid.

<sup>10</sup> Fenwick *et al.*, 1990

shoot elongation, when the thickening roots play an important role as a storage organ. This suggests that glycyrrhizin may participate in the development and maintenance of the thickening main roots as a storage organ.”<sup>11</sup>

Due to this, the plants are usually harvested after at least two years of growth to ensure high glycyrrhizin content. Even though the liquorice extract used in Chinese medicine is obtained from a separate species, the main bioactive component remains the same, i.e. glycyrrhizin is still the desired constituent in the extract. Glycyrrhizin has been estimated to be 50-200 times as sweet as sucrose<sup>12</sup>, hence its salts are widely used as sweeteners, aromatisers in sweets, drugs, beverages, chewing gums, chewing tobacco and toothpastes<sup>13</sup> (Fig. 2).



**Figure 2:** Various products containing liquorice extract. In the bottom left corner, a bag of dried root of *Glycyrrhiza glabra*, and on the right, a closeup of the dried roots (bought in a health food store in Helsinki). Leena Rantala, 2008.

<sup>11</sup> Hayashi *et al.*, 1998

<sup>12</sup> Blomberg & Hallikainen, 1993

<sup>13</sup> Stormer *et al.*, 1993

### 3 A brief history of liquorice

The earliest evidence of its employment lying in the tomb of King Tutankhamen, liquorice may well be one of the herbal remedies with the widest variety of uses in its history. Liquorice was used in ancient Egypt in the making of an iced beverage, *Mai Sus*, which is widely consumed still today. In ancient Greece and Rome it was used commonly as a tonic and cold remedy, in addition to being helpful in treating asthma and healing wounds when mixed with honey. In the first century B.C., Pliny the Elder claimed that in the form of a lozenge, liquorice clears the voice, postpones hunger and thirst, as well as serves as a remedy for healing sores of the mouth, warts of the bladder, pains in the kidneys, and ulcerous sores of the genitals.<sup>14,15</sup>

The ancient Hindus believed that liquorice enhanced sexual performance, while further East the ancient Chinese used liquorice to provide them with strength and endurance. *G. glabra* has been cultivated in England since 1562 and ever since it has been used to soften the skin, smoothen inflamed or irritated mucous membranes, loosen phlegm in the respiratory tract, as well as increase the discharge of urine.<sup>16</sup>

### 4 Glycyrrhizin in metabolism

Liquorice and other liquorice-derived compounds, for example carbenoxolone<sup>17</sup>, have long been used to treat people with peptic ulcers (painful ulcers in the gastrointestinal tract) and Addison's disease (an endocrine disorder involving insufficient production of steroids due to malfunction of the adrenal cortex)<sup>18</sup>, among other diseases.<sup>19,20</sup> In humans, the majority of orally administered glycyrrhizin is hydrolysed to glycyrrhetic acid

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<sup>14</sup> Davis & Morris, 1990

<sup>15</sup> Leppänen, 2004

<sup>16</sup> Davis & Morris, 1990

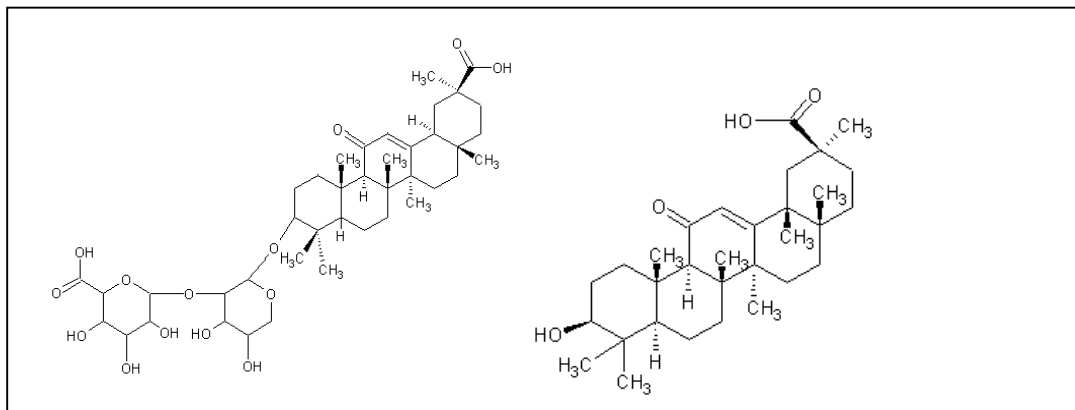
<sup>17</sup> Carbenoxolone (under the trade names Biogastrone and Duogastrone) is a synthetic analog of glycyrrhetic acid, introduced in Great Britain as an anti-ulcer agent. Contrary to glycyrrhizin, carbenoxolone is not hydrolysed, but is taken up in the stomach directly. However, rats have neutral pH in their stomach, so carbenoxolone is not taken up in the acid form, but is hydrolysed and absorbed. Therefore, according to Stormer et al. (1993), rat studies of carbenoxolone have limited relevance to the human situation.

<sup>18</sup> Kauppinen-Mäkelin, 1997

<sup>19</sup> Schambelan, 1994

<sup>20</sup> Baker & Fanestil, 1991

(Fig. 3) by intestinal bacteria such as *Eubacterium* sp. Strain GLH<sup>21,22</sup>. Glycyrrhetic acid then acts in several parts of the body, for example the gastrointestinal tract and the kidney. Studies made in the 1950s revealed that the versatility of liquorice extract as an herbal remedy was due to the fact that glycyrrhetic acid is able to inhibit various enzymes.



**Figure 3:** Molecular structures of glycyrrhizin and glycyrrhetic acid respectively.  
Leena Rantala, 2008

Enzymes are biological catalysts that, by lowering the activation energy and without being consumed in the process, speed up reactions that would normally happen too slowly. Enzymes may be inhibited by either blocking the active site, or by deforming the structure (and leaving the active site impaired) via binding to the enzyme otherwise. Based on studies made on humans and rats, it has been found that glycyrrhetic acid inhibits the enzymes 15-hydroxyprostaglandin dehydrogenase,  $\Delta^{13}$ -prostaglandin reductase and 11 $\beta$ -hydroxysteroid dehydrogenase (11 $\beta$ -OHS $D$ )<sup>23</sup>. 15-hydroxyprostaglandin dehydrogenase and  $\Delta^{13}$ -prostaglandin reductase are involved in prostaglandin metabolism, while 11 $\beta$ -OHS $D$  is responsible for catalysing the conversion of cortisol to cortisone in the kidney (in rodents, corticosterone to 11-dehydrocorticosterone).

#### 4.1 Metabolism of prostaglandins

Prostaglandins are hormone-like lipid compounds that are synthesised from fatty acids and have several functions. One function of prostaglandins in the gastrointestinal tract is

<sup>21</sup> Akao et al., 1988

<sup>22</sup> Stormer et al., 1993

<sup>23</sup> Baker, 1994

to stimulate secretion of mucous and cell proliferation, which in turn stimulate the healing of peptic ulcers. However, prostaglandins  $E_2$  and  $F_{2\alpha}$  are oxidised<sup>24</sup> to inactive metabolites (products or participants in metabolic processes): this process is catalysed by the enzyme 15-hydroxyprostaglandin dehydrogenase. The unsaturated bonds within these ketoprostaglandins are reduced<sup>25</sup> by  $\Delta^{13}$ -prostaglandin reductase, after which they undergo final metabolism and are eliminated in the urine.<sup>26</sup>

#### 4.2 Glycyrrhetic acid as an inhibitor

While glycyrrhizin-containing substances have been successful in healing peptic ulcers and Addison's disease, certain negative side effects have been revealed. These pharmacological properties are mainly due to the inhibitory effects of glycyrrhetic acid: it inhibits several enzymes mentioned previously. The fact that they may all be inhibited by one compound, as well as the similarities in structure of these enzymes, suggest that they may have evolved from the same ancestor<sup>27</sup>.

##### *4.2.1 Prostaglandin enzymes: 15-hydroxyprostaglandin dehydrogenase and $\Delta^{13}$ -prostaglandin reductase*

By inhibiting 15-hydroxyprostaglandin dehydrogenase and  $\Delta^{13}$ -prostaglandin reductase, prostaglandin metabolism is stopped. As prostaglandin metabolism is stopped, the concentration of prostaglandins in the stomach is increased significantly. Carbenoxolone thus promotes the healing of ulcers via increased secretion of mucous and cell proliferation, due to the increase in prostaglandin concentration.

##### *4.2.2 Glucocorticoid enzyme: 11 $\beta$ -hydroxysteroid dehydrogenase*

11 $\beta$ -OHS is an enzyme that catalyses the conversion of cortisol to cortisone, and vice versa. It is located in renal aldosterone target cells, has an unusually high substrate affinity and is very abundant; according to Náray-Fejes-Tóth & Fejes-Tóth (1994) this enzyme may be "responsible for endowing mineralocorticoid target cells with aldosterone selectivity." In other words, as glucocorticoids are much more abundant,

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<sup>24</sup> Oxidation is defined as the loss of electrons (also as the addition of oxygen to a substance).

<sup>25</sup> Reduction is the addition of hydrogen to a substance, also defined as the gain of electrons.

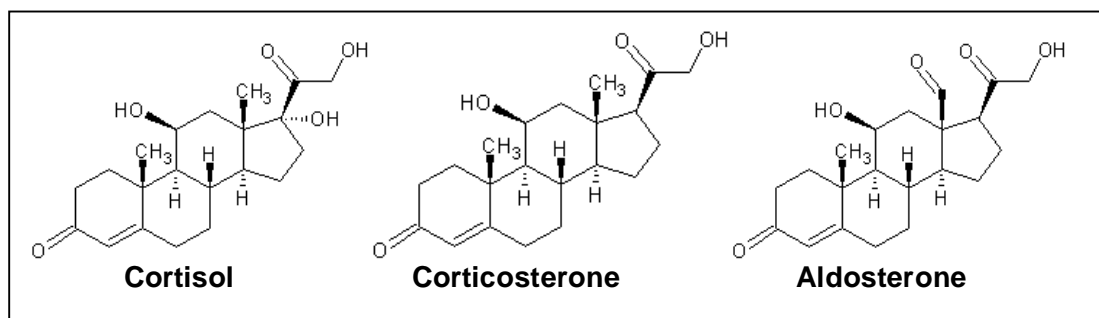
<sup>26</sup> Baker, 1994

<sup>27</sup> Baker, 1994

11 $\beta$ -OHS D acts to protect mineralocorticoid receptors (MC-receptors) from occupancy by glucocorticoids such as cortisol, allowing aldosterone to act as the primary steroid controlling the water and electrolyte balance.<sup>28</sup>

#### 4.3 Corticosteroids: cortisol, corticosterone and aldosterone

In the adrenal glands (also known as suprarenal glands for their location above the kidney), cholesterol is synthesised to corticosteroids, a class of steroid hormones produced in the adrenal cortex. Corticosteroids may be divided into two groups: glucocorticoids and mineralocorticoids. Glucocorticoids, such as cortisol, are produced in the zona fasciculata of the adrenal cortex and control carbohydrate, fat and protein metabolism. Mineralocorticoids, such as aldosterone, are produced in the zona glomerulosa and control electrolyte and water levels via promoting sodium retention in the kidney.



**Figure 4:** Molecular structures of cortisol, corticosterone and aldosterone from left to right. Leena Rantala, 2008

Cortisol, corticosterone and aldosterone are very similar in structure (Fig. 4), and thus bind with equal affinity to MC-receptors. However, the plasma levels of glucocorticoids are much higher than those of mineralocorticoids. This leads to a hypermineralocorticoid effect of cortisol, also known as apparent hypermineralocorticoid syndrome.<sup>29</sup> In order to avoid this effect, 11 $\beta$ -OHS D is required to catalyse the conversion of cortisol to the less active cortisone. In rodents, corticosterone is converted to 11-dehydrocorticosterone.

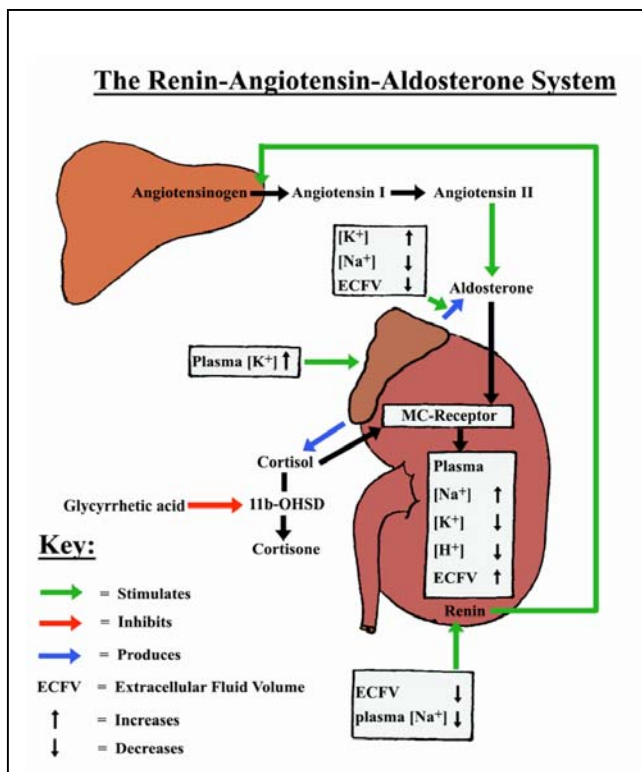
<sup>28</sup> Náray-Fejes-Tóth & Fejes-Tóth, 1994

<sup>29</sup> Stormer *et al.*, 1993

#### 4.4 The renin-angiotensin-aldosterone system

The hypermineralocorticoid effect of cortisol causes suppression of the renin-angiotensin-aldosterone system (Fig. 5). Aldosterone production is regulated by adrenocorticotropic hormone (ACTH), the plasma potassium level, and the renin-angiotensin-aldosterone system. Renin<sup>30</sup> is an enzyme that is produced in the kidney in response to decreased blood pressure or plasma sodium concentration. Renin catalyses the splitting of angiotensin I from the protein angiotensinogen, which is formed by the liver. Angiotensin I is biologically inactive and is therefore modified further; another enzyme called angiotensinase modifies the peptide composition of angiotensin I by cutting out a dipeptide (His-Leu) from the carboxyl-terminal end of the chain. This yields angiotensin II, which is the most powerful inducer of high blood pressure known.<sup>31</sup>

The hormone angiotensin II plays a vital role in controlling blood pressure as it causes the blood vessels to contract (this is known as vasoconstriction). In addition to vasoconstriction, angiotensin II controls blood pressure by stimulating the release of aldosterone, another factor of high blood pressure as it causes the kidney tubules to retain sodium and water.



**Figure 5:** A summarising diagram on the mechanisms involved in the renin-angiotensin-aldosterone system, including the effect of glycyrrhetic acid. Leena Rantala, 2008

<sup>30</sup> Renin is also known as angiotensinogenase

<sup>31</sup> White *et al.*, 1968

## 5 Dose-effect relationships

Before condemning liquorice as too dangerous to consume, one must take into consideration the average consumption and intake of glycyrrhizin. The two women reported of having suffered severe health problems after having eaten liquorice sweets had been consuming huge amounts, 200 g/day and 400 g/day, regularly for a long period of time. Therefore it is necessary to determine a certain safety level as to be able to set limits to risk free consumption of products containing liquorice extract.

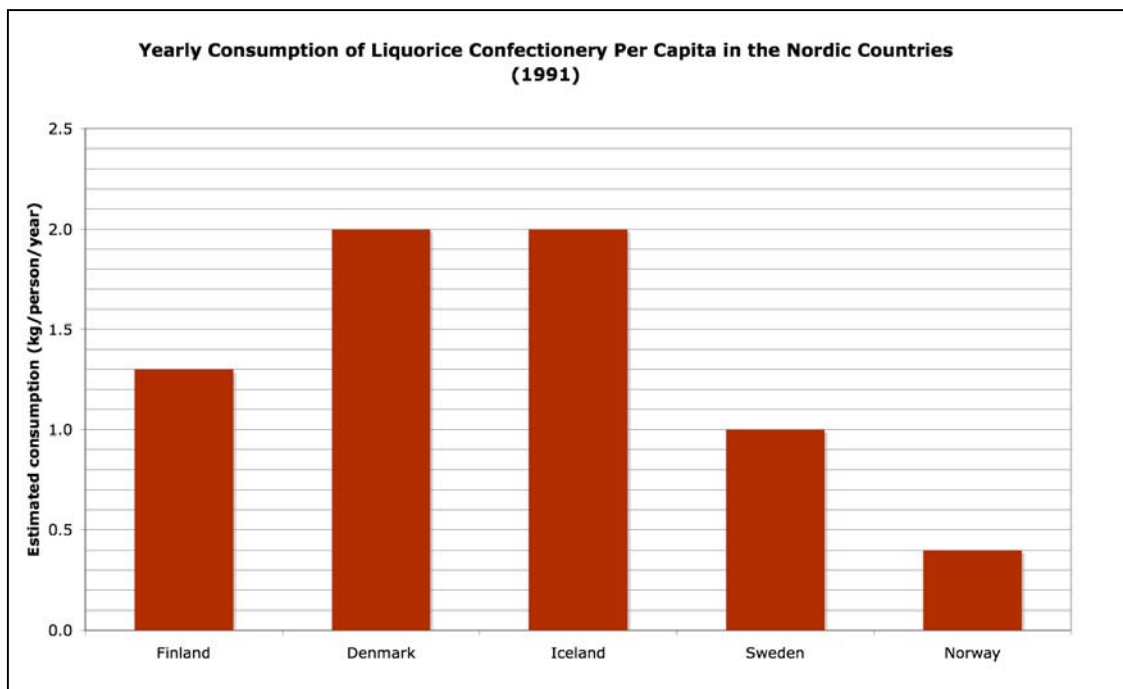
In 1992 the Nordic Working Group on Food Toxicology and Risk Evaluation (NNT) set to investigate the adverse health effects of glycyrrhizin, as well as determine glycyrrhizin levels and average consumption of liquorice confectionery in the Nordic countries. Based on import and production quantities retrieved from the sweets producing industry, the NNT estimated the annual consumption of liquorice sweets in Norway, Denmark, Iceland and Sweden.<sup>32</sup> Similarly in 1993 Blomberg & Hallikainen evaluated consumption of liquorice sweets in Finland for the Finnish National Food Administration (Table 1). Again, evaluation was based on import and production quantities (subtracting the amount of exported goods). Assuming a glycyrrhizin content of 0.2%, the NNT and Blomberg & Hallikainen also estimated the average glycyrrhizin intake, both annually and daily per person (Fig. 6.1 and 6.2).

**Table 1:** Estimated average intake of liquorice confectionery and glycyrrhizin as presented in the Finnish National Food Administration's Research Notes.

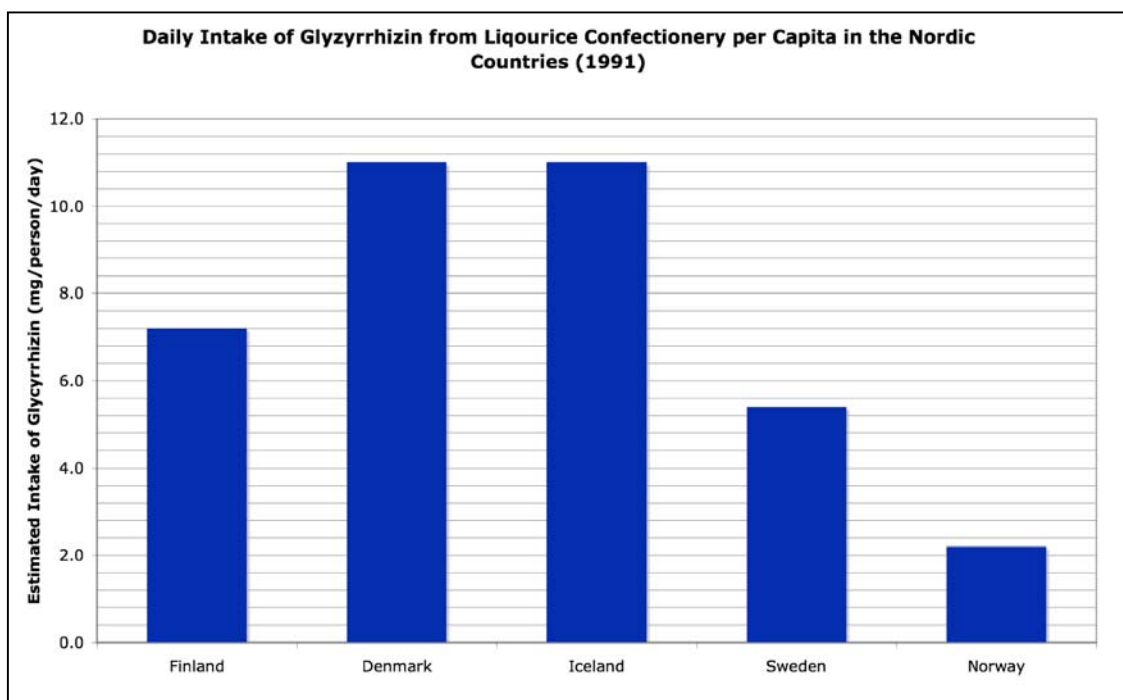
Country		Finland	Denmark	Iceland	Sweden	Norway
Estimated average intake	Liquorice confectionery (kg/person/year)	1.3	2.0	2.0	1.0	0.4
	Glycyrrhizin (mg/person/day)	7.2	11.0	11.0	5.4	2.2

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<sup>32</sup> Stormer *et al.*, 1993



**Figure 6.1:** Comparison of estimated yearly consumption of liquorice confectionery (kg/person) within Nordic countries in 1991. Values are based on the Finnish National Food Administration's report as compiled by Blomberg & Hallikainen (1993).



**Figure 6.2:** Comparison of estimated daily glycyrrhizin intake (g/person) within Nordic countries in 1991. Values are based on the Finnish National Food Administrations Research Notes as compiled by Blomberg & Hallikainen (1993).

As these figures were obtained over 15 years ago, I set to obtain more recent figures for Finnish consumption of liquorice sweets. After contacting several major sweets manufacturers (Kouvolan lakritsi Oy, Cloetta-Fazer Oy, Oy Panda Ab, Halva Oy Ab), the sales representative of Halva Oy Ab, was able to give approximations on the share liquorice sweets hold in the Finnish sweets market. According to their database, bags of liquorice sweets hold 10% of the whole sweets market in Finland. This amounts to 3 000 tonnes of sweets. In addition to traditional bags of sweets, 550 tonnes of liquorice is sold as bars. If these amounts are added together and divided by the population (about 5.3 million<sup>33</sup>), we get an average consumption of 0.7 kg/person/year. Assuming the average glycyrrhizin content to be 0.2%, we get an average yearly intake of 1.3 g/person, or a daily intake of 3.7 mg/person (Tables 2.1 and 2.2).

**Table 2.1:** Estimated sales figures of liquorice sweets in Finland, as provided by one of Finland's major sweets companies, Halva Oy Ab, in July 2008.

Type of confectionery	Quantity sold (tonnes/year)	Percentage share on Finnish sweets market (%)
<b>Bags of sweets</b>	3 000	10
<b>Liquorice bars</b>	550	2
<b>Total</b>	3 550	12

**Table 2.2:** Comparison between estimated values of Finnish consumption.

Source	Liquorice confectionery (kg/person/year)	Glycyrrhizin (g/person/year)	Glycyrrhizin (mg/person/day)
Finnish National Food Administration (1993)	1.0	2.0	5.4
Estimated by Halva Oy Ab (2008)	0.7	1.3	3.7

In the shade of these approximations and motivated by studies of case reports where patients have demonstrated adverse effects, the NNT strove to set a lowest observable adverse effect level (LOAEL). According to their report, the most sensitive individuals showed symptoms at a regular (more than 1-2 weeks) daily intake of 100 mg

<sup>33</sup> Finnish Population Register Center, 2008

glycyrrhizin, amounting to about 50 g of sweets per day. Even with incomplete approximations on Finnish consumption, it is safe to assume that the average intake is far below the LOAEL.

## 6 Conclusion

Having reviewed the renin-angiotensin-aldosterone system, relevant glucocorticoids, and the enzymes inhibited by glycyrrhetic acid, we may now identify the pathways involved in the hypertension-inducing mechanism of liquorice-derived compounds.<sup>34</sup>

By inhibiting the conversion of cortisol to cortisone, glycyrrhizin's aglycone, glycyrrhetic acid, causes the MC-receptors of the kidney to be occupied by cortisol. The over occupation of MC-receptors by cortisol leads to the apparent hypermineralocorticoid effect. This effect will cause sodium retention, potassium loss, increased water retention, expanded extracellular fluid volume, and the elevation of blood pressure. As renin production is normally stimulated by decreased extracellular fluid and low sodium concentrations in the plasma, the symptoms of the apparent hypermineralocorticoid effect will act as negative feedback. As the amount of renin in the kidney decreases, less and less angiotensinogen is converted to angiotensin I. This ultimately causes the suppression of the whole renin-angiotensin-aldosterone system as the synthesis and secretion of aldosterone is reduced.<sup>35</sup>

The inhibitory effect of  $11\beta$ -OHSD is reversible and the aforementioned symptoms will eventually disappear; yet the subsequent effects of suppressing the renin-angiotensin-aldosterone system may last for one to two months even after intake of glycyrrhizin has ceased.<sup>36,37</sup>

When looking at the figures representing liquorice consumption and glycyrrhizin intake, one must keep in mind that they are only approximate. First of all, liquorice consumption is not divided evenly over the whole population, for example children under 3 are unlikely

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<sup>34</sup> See Appendix A for summary of substances involved in the metabolic pathways under study.

<sup>35</sup> Stormer *et al.*, 1993

<sup>36</sup> Stormer *et al.*, 1993

<sup>37</sup> Tikkanen, 2007

to consume as much liquorice as a 30-year-old woman. This would mean that as part of the population consumes no liquorice at all, to compensate, the rest consume more than the average values would indicate.

Glycyrrhizin content also varies between brands (important information that is often unavailable to the consumer) and these values do not take into account glycyrrhizin intake from other sources, such as cough medicine and products of the tobacco industry. This is a significant fault as at least in the US, 90% of the liquorice supply is used in the tobacco industry<sup>38</sup>, and certain products, for example liquorice flavoured chewing gum, tea and cough suppressants, may contain much higher amounts of glycyrrhizin<sup>39</sup>. Also, the figures provided by Halva Oy Ab only included traditional bags and bars of liquorice. Yet at least in Finland liquorice extract is found in so many different products that if, on average, a person acquires 3.7 mg of glycyrrhizin daily from only the abovementioned products, we may assume that the total intake of glycyrrhizin may be much higher.

To fully determine and understand the magnitude of glycyrrhizin intake, further research is needed. A comprehensive overview on the quantity of liquorice extract used in products other than confectionery, such as tobacco and other nicotine products, would provide greater insight into the true amounts of glycyrrhizin consumed. Using this information, it would be easier to define the true risks, or possible lack of them, associated with the consumption of products containing liquorice-derived compounds. The LOAEL set by the NNT should perhaps be revised to ensure it matches current values.

Especially in a time when sweets come in 500g bags, it is fairly easy to exceed the LOAEL temporarily, as was seen in the cases described above. Children are often considered to be the most vigorous consumers of candy, but parents should not be required to research scientific journals in order to know whether or not they can safely buy their child a bag of popular sweets. As the sensitivity to the hypertension-inducing effects varies greatly among individuals, it is safe to assume that small children are more

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<sup>38</sup> Fenwick *et al.*, 1991

<sup>39</sup> Stormer *et al.*, 1993

sensitive than grown-ups, and that even occasional consumption may have noticeable effects.<sup>40</sup>

Certainly, it is not the consumer's responsibility to find out what is safe and what is not. Products containing ambiguous substances such as glycyrrhizin should most definitely have clear labels and guidelines indicating possible adverse effects. During my inquiries on various products containing liquorice extract, I came across specialised stores with products, usually herbal teas and natural remedies, that contained explicit tags stating that people suffering of high blood pressure should take care when consuming these products. This is a policy that should most definitely be followed with sweets too, as we may presume that a great deal of harmful quantities of liquorice extract come from the sweets industry.

Further research should not however only be concentrated on the negative. After all, *Glycyrrhiza glabra* has offered us with remedies for various illnesses during centuries and humans are, and always will be, inevitably tied to nature. Therefore future investigations should strive to increase knowledge and make us more aware, instead of just more afraid. We may be able to take advantage of the benefits liquorice extract has to offer by being cautious of possible adverse effects at the same time. As glycyrrhetic acid is capable of inhibiting several enzymes, it has been suggested that these enzymes would have evolved from the same ancestor. Discovering other enzymes homologous to these may offer interesting possibilities in discovering additional uses for the inhibitory properties of liquorice-derived compounds.

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<sup>40</sup> Tikkanen, 2007

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## 8 Appendices

**Appendix A:** Summary of substances involved in the metabolic pathways under study (sites of function and functions listed are within the context of the research), as compiled by Leena Rantala on the basis of works by Baker (1994), Kent (2000), N aray-Fejes-T oth & Fejes-T oth (1994), Schambelan (1994), Stormer *et al.* (1993), and White *et al.* (1968).

Substance	Type of protein	Site of production	Site of function	Function
Cortisol	Steroid hormone (glucocorticoid)	Adrenal cortex (zona fasciculata)	Kidney	Controls carbohydrate, fat and protein metabolism
Corticosterone	Steroid hormone (glucocorticoid)	Adrenal cortex (zona fasciculata)	Kidney (mainly rodents)	Regulation of fuel metabolism in rodents
Cortisone	Steroid hormone (corticosteroid)	Adrenal cortex	Kidney	Inactive metabolite
11-dehydrocorticosterone	Steroid hormone (corticosteroid)	Adrenal cortex	Kidney (mainly rodents)	Inactive metabolite
Aldosterone	Steroid hormone (mineralocorticoid)	Adrenal cortex (zona glomerulosa)	Kidney	Controls water and electrolyte balance and blood pressure
11 $\beta$ -hydroxysteroid dehydrogenase (11 $\beta$ -OHS)	Enzyme (oxidoreductase)	[no data obtained]	Kidney	Catalyses conversion between cortisol and cortisone
15-hydroxyprostaglandin dehydrogenase	Enzyme (oxidoreductase)	[no data obtained]	Digestive tract	Catalyses first step of prostaglandin metabolism
$\Delta^{13}$ -prostaglandin reductase	Enzyme	[no data obtained]	Digestive tract	Catalyses second step of prostaglandin metabolism
Renin	Enzyme & hormone	Kidney	Liver	Catalyses conversion of angiotensinogen to angiotensin I
Angiotensinogen	Hormone (endocrine)	Liver	Liver	Renin substrate, is converted to angiotensin I
Angiotensin I	Hormone	Liver	Liver	Inactive precursor of angiotensin II
Angiotensin II	Hormone	Liver	Adrenal gland	Increases blood pressure, stimulates secretion of aldosterone
Adrenocorticotrophic hormone (ACTH)	Hormone	Pituitary gland	Adrenal gland	Stimulates production of corticosteroids