Chapter 15
Cardiovascular Toxicities of Herbal Products: An Overview of Selected Compounds

Pieter van der Bijl Jr. and Pieter van der Bijl Sr.

Abstract The use of herbal products for a wide variety of health and medicinal purposes by all ethnic groups worldwide is prevalent and rising, despite a conspicuous lack of rigorous scientific evidence regarding their safety and efficacy. While these products are frequently considered safe by patients and healthcare practitioners alike, they may cause adverse effects that frequently involve the cardiovascular system. A spectrum of chemical compounds is usually present in these products, some of which cause direct cardiovascular toxicity, and others to which clinically relevant herb-allopathic drug interactions may be attributed when taken concomitantly with conventional therapies. The objective of this chapter is to provide an overview of selected herbs that manifest cardiovascular toxicity and those for which herb-allopathic drug interactions affecting the cardiovascular system have been described. Furthermore, the general principles of diagnosis and management of cardiovascular toxicity of these remedies are also discussed.

Keywords Herbal products • Cardiovascular toxicity • Herb-allopathic drug interactions

Introduction

It has been known for centuries that some plants possess medicinal properties. The ancient Egyptians and Romans recognized the fact that extracts of *Urginea maritima* had diuretic, cardiotonic, expectorant, and emetic properties (Naudé 1997). Furthermore, the medicinal value of *Digitalis purpurea* (foxglove, which contains

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cardiac glycosides) was reported by William Withering in 1785 after observing that patients with dropsy (edema secondary to cardiac failure) could be treated with an extract from this plant (Bessen 1986).

Since time immemorial, herbal medicines have been used as a mainstay of complementary and alternative medicine (CAM), which has experienced a resurgence in Western societies over the past two decades (Hunt et al. 2010; Merrit-Charles 2011; Mugabo et al. 2012). These plant-derived products are used for their beneficial (real or purported) effects in improving health and treating a wide range of clinical conditions including asthma, malignancies, dermatological ailments, epilepsy, acquired immunodeficiency syndrome (AIDS), cardiovascular diseases, diabetes mellitus, coryza, and influenza – as well as pain. Generally, their mechanisms of action are uncertain or unknown, and there is a dearth of clinical efficacy and safety data for these products (Ernst 2007; Sahoo et al. 2010; Cravotto et al. 2010).

It is estimated that worldwide, approximately 25 % of adults in developed countries and >80 % of the population of developing countries use herbal medicines, which are derived from >11,000 species of plants (Chen et al. 2012). Data from the National Health Interview Survey show that the use of non-vitamin, non-mineral dietary supplements was greater than any other complementary health approach used by adults in the U.S. in 2012 (Peregoy et al. 2014). In Europe, the use of CAM is even more prevalent, where studies from 20 countries (representing 69 % of the continent's population) estimate that 56 % of the general population and 52 % of children had used CAM at least once in the year prior to which the survey had been conducted (Zuzak et al. 2013). These figures resemble data from the U.K. obtained from a systematic review in which the average 1-year prevalence of use of herbal medicines was 64.2 % (Posadzki et al. 2012 and 2013). In South Africa, the use of plant-derived products is widespread in the practice of traditional medicine, and it is estimated that some 80 % of the South African population consults traditional healers regularly (Mugabo et al. 2012). These traditional medicines ("muti") are usually administered orally or given as enemas. Laboratory analyses of muti have shown that these preparations often consist of aqueous plant materials, e.g., roots, bark stem, or leaves, sometimes mixed with metallic salts, mushrooms and insects (McVann et al. 1992). Plant components are sometimes pulverized or sliced into small pieces, making botanical identification difficult or impossible.

Notwithstanding many assertions that herbal remedies are safe and lack adverse effects, this is untrue, particularly when they are used in the management of serious conditions (Singh 2009; Hunt et al. 2010). It is well documented that some herbal medicines contain toxic chemical compounds that have direct toxic effects, among others those involving the cardiovascular system (Van der Bijl and Van der Bijl 2012). Furthermore, during the co-administration with allopathic drugs, certain herbal medicines have the potential for herb-drug interactions that can be of significant clinical importance (Chen et al. 2012; Posadzki et al. 2012). Both the direct cardiovascular toxicity and herb-allopathic drug-interactive effects range from being merely inconvenient to life-threatening.

Direct Cardiovascular Toxicity

A selection of some important medicinally used plants that contain cardiovascular toxins are:

Digitalis lanata and *purpurea* (foxgloves), *Convallaria majalis* (Lily of the valley), *Nerium oleander* (common or pink oleander), *Thevetia peruviana* (yellow oleander), *Acokanthera oppositifolia* and *schimperi* (bushman poison bush), *Urginea maritima* and *indica* (squill), *Drimia sanguinea* (sekanama), *Bowiea volubilis* (climbing potato), *Asclepias curassavica* (milkwood), *Strophantus gratus*, *Apocynum cannabinum* (dogbane) and *Cheiranthus cheiri* (wallflower). The abovementioned plants all contain cardiac glycosides, and these chemical compounds can be lethal to both livestock and humans (Botha and Penrith 2008, 2009; Snyman et al. 2011).

The cardiac glycosides, which are highly toxic chemical compounds, are found in a number of plants. These phytochemicals, which occur in the highest concentrations in the plant seeds, consist of an aglycone (structurally related to steroid hormones) linked to one or more sugar molecules. The aglycones of cardiac glycosides can be divided into two chemical groups – the cardenolides and bufadienolides. It is assumed that the general principles of digoxin toxicity also hold true for other glycosides, even though the latter have been less well studied.

The primary pharmacological effect of cardiac glycosides is to inhibit the Na^+/K^+-ATPase exchanger of the myocardiocyte that increases intracellular Na^+ concentration, thus reducing the amount of Ca^{2+} pumped out of the cell by the Na^+/Ca^{2+} exchanger (Hauptman and Kelly 1999; Kumar et al. 2013). Glycosides bind to the extracellular α-subunit (the enzyme being a heterotrimer consisting of α-, β- and γ-subunits) of the Na^+/K^+-ATPase exchanger (Hauptman and Kelly 1999). Consequently, the intracellular Ca^{2+} concentration rises, thereby occasioning positive inotropy (Fig. 15.1); this also appears to be the mechanism of tachydysrhythmogenesis. Excess Ca^{2+} remains intracellularly after the cell has repolarized, and this elicits a transient, inward Na^+ current, known as I_{ti} (via nonspecific cation channels), which in turn leads to a delayed afterdepolarization (during phase 4 of the cardiac action potential) (Hauptman and Kelly 1999) (Fig. 15.2).

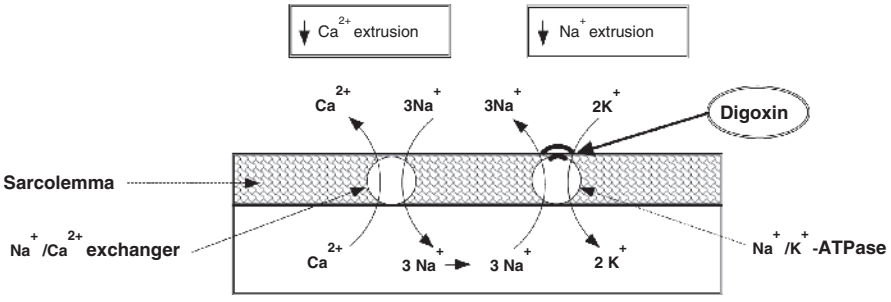

Fig. 15.1 The mechanism of action of cardiac glycosides, e.g., digoxin

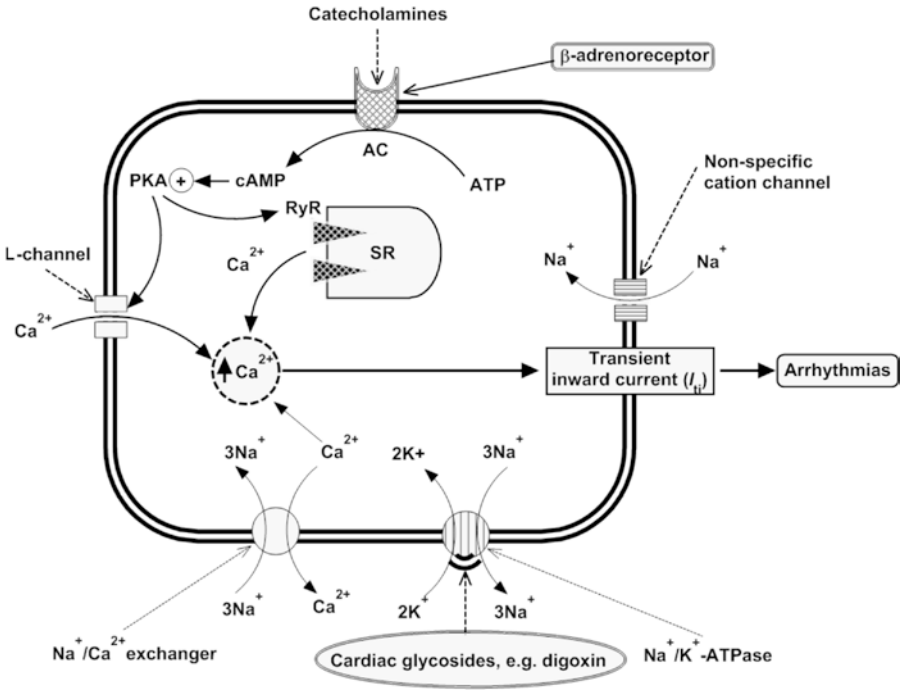

Fig. 15.2 The role of catecholamines, cardiac glycosides and Ca^{2+}-overload in the genesis of delayed afterdepolarizations. Cyclic adenosine monophosphate (cAMP); adenyl cyclase (AC); adenosine triphosphate (ATP); protein kinase A (PKA); ryanodine receptor (RyR); sarcoplasmic reticulum (SR); ligand-gated cation channel (L-channel)

A secondary pharmacological effect is a depressant effect on the atrioventricular node via central vagal stimulation (causing decreased dromotropy of the atrioventricular node, as well as an increase in its refractory period), which contributes to pathological bradycardias, together with a direct, depressant effect on the atrioventricular node. Catecholamines potentiate glycoside toxicity via stimulation of β-adrenoreceptors, which lead to the production of cyclic adenosine monophosphate (cAMP) by means of adenylate cyclase. cAMP in turn activates protein kinase A, which phosphorylates the α-subunit of the L-type Ca^{2+} channel (embedded in the cell membrane), and the ryanodine receptor in the sarcoplasmic reticulum, leading to elevated intracellular Ca^{2+} levels, which then follow the final common pathway of delayed afterdepolarizations (Lubbe et al. 1992) (Fig. 15.2). Glycoside toxicity is potentiated (via delayed afterdepolarization) by electrolyte disturbances (especially hypokalemia, but also hypomagnesemia and hypercalcemia), ischemia, reperfusion injury, and increased ventricular wall stress.

Cardiac glycosides have very narrow therapeutic indices, and acute toxicity is most commonly associated with ingestion of plant material, although chronic toxicity (manifesting with anorexia, for example) may also be seen. In cases of acute intoxication, nausea, emesis (effected via the chemoreceptor trigger zone, rather

than due to a direct effect on the gastrointestinal system, but also attributed to parasympathomimetic effects) and abdominal pain typically occur, as well as central nervous system effects including lethargy, weakness, and visual disturbances – primarily chromatopsia, especially xanthopsia – but also scotomas and halos. A host of arrhythmias, including conduction disturbances and/or bradycardias (Wenckebach A & B-sinoatrial block and atrioventricular block), tachycardias (ectopic atrial tachycardia, atrial fibrillation, junctional tachycardia, bifascicular ventricular tachycardia, ventricular fibrillation) and other electrical disturbances (accelerated idioventricular rhythm and bigeminy) can manifest. Some are challenging to diagnose and are often overlooked, e.g., ectopic atrial tachycardia, where the focus is usually in the superior right atrium, producing P-waves that are similar in morphology to those of sinus rhythm, and also depolarizing the atria in the same direction. Others are fairly unique and easier to recognize, e.g., bifascicular ventricular tachycardia (a life-threatening rhythm with alternating left- and right axes due to the focus originating in the anterior and posterior fascicles of the left bundle branch, respectively) and unexpected regularization of ventricular impulses due to a junctional tachycardia that appears on a background of atrial fibrillation (Hauptman and Kelly 1999).

Aconitum carmichaeli *("chuanwu"),* Aconitum kuznezoffii *("caowu")*

Aconitine and related alkaloids of aconite (mesaconite and hyperconitine) are constituents of *Aconitum* species of plants, and they are used as analgesics/anti-inflammatories, particularly in China and Japan. The roots and root tubers of these plants are typically consumed as vegetables and used in the preparation of herbal soups and meals (Singhuber et al. 2009; Kang et al. 2012). The latter are, in contrast to aqueous decoctions (mashing and boiling), a more agreeable way of ingesting the herbal product. The wild plant, especially the raw roots and root tubers, are very toxic due to the presence of high concentrations of *Aconitum* alkaloids, which are hydrolyzed into less toxic and non-toxic derivatives by soaking and boiling (Chan 2009). However, even after processing, concentrations of these alkaloids (which are potent cardio- and neurotoxins) can remain high enough to cause poisoning.

Both the cardio- and neurotoxicity of aconitine and its related alkaloids are due to their effects on voltage-sensitive Na^+-channels of myocardial, neural, and muscle cells. Aconitine and mesaconitine bind strongly to the open state of voltage-sensitive Na^+-channels at site 2, causing a persistent activation of these channels and rendering them refractory to excitation (Chan 2009; Friese et al. 1997). Delayed afterdepolarizations (i.e., triggered activity) induce arrhythmias via the downstream inhibition of the Na^+/Ca^{2+}-exchanger by excessive intracellular Na^+, causing intracellular Ca^{2+} overload (similar to glycosides). Tachycardias (ventricular tachycardia – including bifascicular tachycardia, *torsades de pointes*, and ventricular fibrillation), bradycardias/conduction disturbances (sinus bradycardia, asystole) and other rhythm disturbances (ventricular ectopics, junctional rhythms) have been linked to

aconitine toxicity, and are often refractory to treatment (Lu and De Clerck 1993; Tai et al. 1992; Chan 2009). The ventromedial nucleus of the hypothalamus is affected by aconitine in rats, causing modulation of the autonomic nervous system with bradycardia and hypotension (Yamanaka et al. 2002; Hirasawa et al. 1998).

Following ingestion of toxic doses of aconitine and/or related alkaloids of aconite, the toxidrome manifests in the neurological (facial and limb paresthesia/weakness), gastrointestinal (nausea, emesis and abdominal cramps), and cardiovascular systems.

Hyoscyamus niger *(henbane)*

All parts of this plant contain tropane alkaloids in varying quantities (e.g., atropine, hyoscyamine and scopolamine), which competitively inhibit the muscarinic effects of acetylcholine and block impulse transmission in the parasympathetic nervous system, resulting in the classic anticholinergic syndrome (Spoerke et al. 1987). However, other potentially toxic natural compounds, e.g., coumarins, flavonoids, sterols, tannins, and terpenes have also been found in *Hyoscyamus niger* extracts (Khan and Gilani 2008). The toxidrome comprises central nervous system manifestations (e.g., seizures) and peripheral vasodilatation (dry, warm skin).

The primary cardiac effect of Henbane is sinus tachycardia due to the vagolytic effect of the alkaloids. This is not dangerous per se, but might be poorly tolerated by those with underlying heart disease. Even though the toxidrome includes peripheral vasodilatation, paradoxical hypertension (without a specific mechanistic explanation) has been described in overdose (Li et al. 2011; Urkin et al. 1991).

Lycopodium serratum *("jin bu huan")*

Jin bu huan is a popular Chinese herbal medication that has been used for centuries as a mild sedative, a decongestant, and as a treatment for conditions ranging from asthma and bronchitis to nictalopia, delirium, epilepsy, vertigo, pyrexia and inflammation, arthritic and orthopedic pain, and gastrointestinal complaints. While the basis for the sedative, analgesic, and anti-inflammatory properties of this plant material is unclear, it contains levo-tetrahydropalmitine and pyrrolozidine alkaloids. The former has sedative effects, possibly due to it being a dopamine receptor and a Ca^{2+}-channel antagonist (Larrey 1997). Unintentional overdoses have been shown to cause central nervous system and respiratory depression with rapid onset of transient, severe sinus bradycardia (Centers for Disease Control and Prevention 1993; Horowitz et al. 1996).

Mitragyna speciosa *("kratom"/"ketum")*

The traditional use of this tropical herb plant dates back many centuries and has its origins in Southeast Asian countries e.g., Thailand and Malaysia; it is known as "ketum" in Malaysia and "kratom" in Thailand. Natives of these countries traditionally consume the leaves by masticating, smoking, or drinking them (as a tea) for their stimulant and euphoric effects (Babu et al. 2008). In recent times, kratom has become popular for recreational purposes and as a substitute in cases of opioid dependency, as well as a treatment for systemic hypertension. The plant contains more than 40 compounds in its leaves, including many alkaloids such as mitragynine (once thought to be the primary active constituent), mitraphylline, and 7-hydroxymitragynine (which is currently the most likely candidate for the primary active chemical in the plant), and mitragynine pseudoindoxyl (Adkins et al. 2011; Chittrakarn et al. 2010; Prozialeck et al. 2012). Other active compounds in *Mitragyna speciosa* include raubasine (best known as a constituent of *Rauwolfia serpentina*), rhyncophylline, and corynantheidine among others (Takayama et al. 2002). Acute toxic effects of kratom appear to be related to its stimulant (e.g., anxiety and aggression) and opioid (e.g., nausea and sedation) activities.

Withdrawal symptoms that have been found are similar to those of other opioids; they include irritability, dysphoria, nausea, insomnia, oscitation, rhinorrhea, myalgia, diarrhea, arthralgia, and hypertension (Prozialeck et al. 2012). The fear of kratom products being adulterated or interacting with other drugs has been raised.

The primary cardiovascular manifestation appears to be systemic hypertension (the mechanism of which is unknown), which may be especially detrimental when kratom is taken for lowering blood pressure.

Tussilago farafara *(coltsfoot)*

This herb, also known as "coltsfoot," belongs to the family *Asterracea* and is commonly found in Europe, Asia, and the Americas. It has been ingested as a tea or syrup and topically applied for respiratory and cutaneous complaints, viral infections, influenza, coryza, and rheumatic conditions (Vogl et al. 2013). Toxic pyrrolizidine alkaloids are present in the plant. Apart from hepatotoxicity, these alkaloids are associated with cor pulmonale (likely due to its inhibition of nitric oxide release and subsequent pulmonary vasoconstriction), while left ventricular dysfunction and medial thickening of the coronary arteries have been described in rats after ingestion (Joint FAO/WHO Food Standards Programme Codex Committee on Contaminants in Food 2011). Furthermore, the administration of monocrotaline (a toxic pyrrolizidine alkaloid of plant origin) to rats caused myocarditis, independent of the degree of pulmonary hypertension (Akhavein et al. 2007). Coltsfoot has been found to cause a hypertensive response in humans (Li and Wang. 1988).

Erythroxylum coca *(Coca)*

This plant is one of two species of cultivated Coca that are native to the Andean region in western South America. The leaves of the *Erythroxylum coca* bush have been chewed by native South American tribes for thousands of years for their analgesic, anorexogenic, and stimulatory effects (Schwartz et al. 2010). The active ingredient, cocaine (an alkaloid), was purified over a century ago and used in tonics and elixirs. It is a highly addictive stimulant, making this alkaloid one of the most popular drugs of abuse. A freebase form ("crack") became a sought-after drug some 30 years ago. Although cocaine use occurs primarily in the Americas, Europe, and Oceania, the evidence regarding the extent of its use in Africa and Asia is unestablished (United Nations Office on Drugs and Crime 2014). However, some pockets of emerging use in these regions may be developing. Worldwide, there seems to be a slight decline in its use due to a decrease in the overall global availability of the alkaloid (United Nations Office on Drugs and Crime 2014).

Cocaine (benzoylmethylecgonine, $C_{17}H_{21}NO_4$) is a potent sympathomimetic and local anesthetic. The alkaloid is dissolved in hydrochloric acid to form a water-soluble hydrochloride salt that can exist in a crystalline, powder, or granular form. When a solution of the hydrochloride salt is alkalinized and extracted with ether, and the latter has evaporated, a non-salt (freebase) form results. The freebase form melts at 98 °C, making a crackling sound and has therefore been given the "street" name of "crack" (Maraj et al. 2010).

All mucous membranes of the body absorb cocaine well, the compound typically being inhaled intranasally ("snorted"), but the alkaloid can also be administered by intramuscular and intravenous routes. The onset of action is rapid (seconds to minutes), depending on the route of administration, and peak effects as well as the duration of action may range from several minutes to 1.5 h (Maraj et al. 2010). In humans, elimination $t_{½}$ ranges from 30 to 60 min, the metabolism of cocaine being mainly by plasma and hepatic cholinesterases. The water-soluble metabolites, benzoylecgonine and ethylmethylecgonine, as well as 5-10 % of unchanged cocaine are excreted in the urine. While unchanged cocaine is usually not found in urine after 6 h, the metabolites are, with benzoylecgonine being detected in urinary samples of chronic abusers for as long as 22 days after their last dose (Maraj et al. 2010). This may be important clinically, for example in diagnosing a myocardial infarct following recent abuse of this alkaloid.

By inhibiting catecholamine re-uptake, cocaine powerfully stimulates the sympathetic nervous system – it also sensitizes adrenergic nerve endings to norepinephrine (Riezzo et al. 2012) (Fig. 15.3). Cocaine releases endothelin-1 from endothelium and inhibits nitric oxide production – a combination that leads to vasoconstriction and a rise in systemic blood pressure (Wilbert-Lampen et al. 1998; Mo et al. 1998). It causes coronary artery vasoconstriction (more pronounced in atherosclerotic than normal vessels), smooth-muscle cell plaque rupture (in contrast to

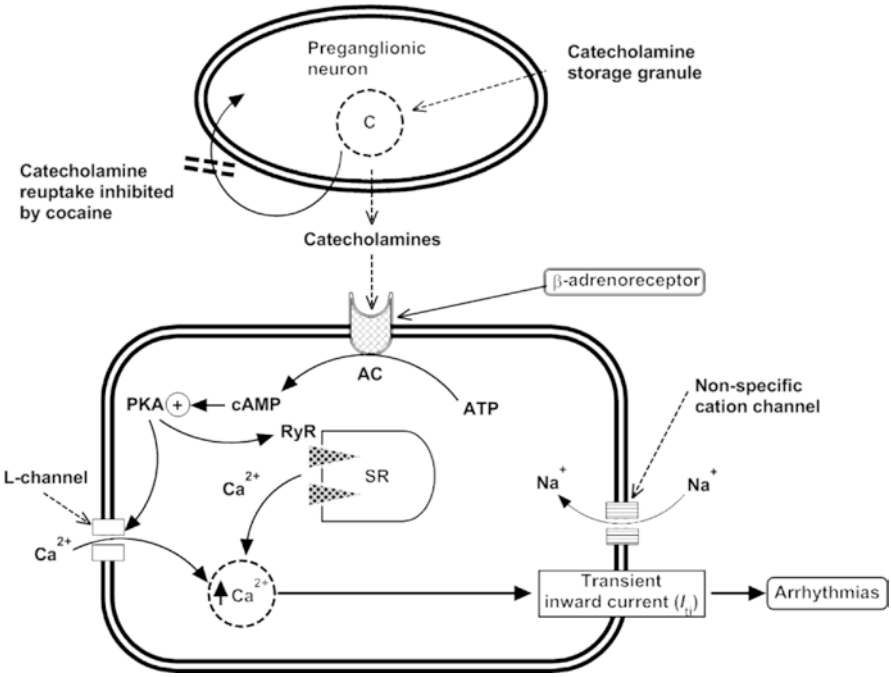

Fig. 15.3 The role of cocaine and Ca^{2+}-overload in the genesis of delayed afterdepolarizations. Cyclic adenosine monophosphate (*cAMP*); adenyl cyclase (*AC*); adenosine triphosphate (*ATP*); protein kinase A (*PKA*); ryanodine receptor (*RyR*); sarcoplasmic reticulum (*SR*); ligand-gated cation channel (*L-channel*); catecholamine (*C*)

atherosclerotic plaque in those with traditional risk factors for atherogenesis), thrombocyte activation, aggregation, degranulation, and thrombus formation, which lead to coronary syndromes and life-threatening arrhythmias (Heesch et al. 2000; Flores et al. 1990; Schwartz et al. 2010). Long-term abuse causes endothelial dysfunction of the coronary arteries, a known sensitizer for catecholamine-induced vasoconstrictor effects (Havranek et al. 1996; Vita et al. 1992). Cardiac ischemia is induced by the supply-demand mismatch, which reflects coronary vasoconstriction and increased O_2-requirements due to increased heart rate (tachycardia) and blood pressure (Lange et al. 1989).

By blocking K^+-channels and Na^+-channels, as well as by intracellular Ca^{2+}-overload (on the basis of sympathetic stimulation of β-adrenoreceptors, leading to formation of protein kinase A, which translates into intracellular Ca^{2+}-overload and delayed afterdepolarizations – similar to glycoside toxicity), cocaine has proarrhythmic effects in the absence of ischemia (Riezo et al. 2012). It is documented to cause a spectrum of arrhythmias, e.g., monomorphic ventricular tachycardia, *torsades de pointes*, ventricular fibrillation, atrioventricular block and asystole (Bauman et al. 1994; Hsue et al. 2007; Schwartz et al. 2010) (Fig. 15.3).

Cocaine causes myocardial dysfunction via (1) ischemia and infarction, (2) myocarditis (possibly engendered by infectious agents or adulterants that are co-administered, and (3) direct toxic effects. Direct cardiac damage is caused by mitochondrial toxicity, which in turn is due to two mechanisms, i.e., oxidative stress and Ca^{2+}-overload. Sympathetic stimulation of β-adrenoreceptors leads to formation of protein kinase A, causing intracellular Ca^{2+}-overload (similar to cardiac glycoside toxicity). Oxidative stress is occasioned by transformation of catecholamines into aminochromes, which partake in redox reactions in mitochondria and lead to the formation of free radicals. Mitochondrial permeability increases due to the above-mentioned mechanisms, and apoptotic and necrotic myocardiocyte death follows (Liaudet et al. 2014). Chronic use of this alkaloid may lead to left ventricular hypertrophy (likely due to systemic hypertension), dilated cardiomyopathy, and Takutsubo cardiomyopathy and a final common pathway of systolic as well as diastolic cardiac dysfunction (Schwartz et al. 2010; Arora et al. 2006; Daniel et al. 2007; Chambers et al. 1987). Reversible myocardial depression can also manifest after acute intoxication (Schwartz et al. 2010).

Aortic dissection is temporally related to cocaine abuse, and it is assumed to be a reflection of increased systemic arterial pressure. It should be considered in the differential diagnosis of a patient presenting with recent cocaine use and chest pain, in addition to coronary syndromes. Infective endocarditis occurs more frequently than what may be attributed to the intravenous route of administration per se. This may be due to direct endothelial damage caused by high arterial pressures and tachycardia and/or the direct immunosuppressive effects of cocaine, on which intravenous injection is superimposed.

Citrus aurantium *(bitter orange)*

The peel, flower, leaf, fruit, and fruit juice from this citrus tree are used to prepare medicine, and the oil is prepared from the peel. The plant and its products are used as a herbal medicine for a wide variety of conditions ranging from gastrointestinal complaints and obesity (as an anorexigen), to lowering blood sugar (as an antidiabetic agent).

The extracts from *Citrus aurantium* contain tyramine metabolites N-methyltyramine, octopamine, and synephrine (Gange et al. 2006). These compounds are chemically similar to synephrine and stimulate α_1-adrenergic receptors, causing peripheral vasoconstriction, systemic hypertension and tachycardia. After the banning of ephedra in the U.S. and Canada, bitter orange was substituted into "ephedra-free" herbal weight-loss products (FDA 2004). There have been reports of bitter orange causing acute coronary syndromes and cerebrovascular accidents (National Center for Complementary and Alternative Medicine 2012). After an incident of a healthy young man who suffered an ST-elevation myocardial infarct that was linked to the ingestion of bitter orange, it was discovered that certain manufacturers of dietary supplements substituted ephedra with its chemical congeners from

bitter orange (Thomas et al. 2009). Like most other dietary supplement ingredients, *Citrus aurantium* has not yet undergone proper safety testing, leading to the report by the National Center for Complementary and Alternative Medicine's statement that "there is currently little evidence that bitter orange is safer to use than ephedra" (National Center for Complementary and Alternative Medicine 2012).

Glycyrrhiza glabra *(licorice)*

The genus *Glycyrrhiza* comprises roughly 30 species, of which *Glycyrrhiza glabra* is popularly recognized as licorice due to its sweet taste. Licorice is extracted from the root of this legume, which is similar to peas and beans, and is found in southern Europe, India, and some parts of Asia. Licorice was used as a medicinal herb in ancient Egypt and Greece to relieve symptoms in individuals with adrenal insufficiency, chronic hepatitis, cystitis, gastric ulcers, urolithiasis, and diabetes.

Glycyrrhizin, a triterpenoid consisting of the K^+, Ca^{2+} and Mg^{2+}-salts of glycerrhizic acid, is one of the main active constituents of licorice and, being up to 50 times sweeter than sucrose, is responsible for its sweet taste. The glycyrrhizin content in the roots of the plant is between 2 and 25 %, depending on the species of legume. Chemically, the glycyrrhizin molecule comprises a hydrophobic 5-ring structure (glycyrrhetinic acid) linked to two hydrophilic glucuronic acid molecules. Flavonoids (liquiritin, isoliquiritin, isoflavones, glabridin and hispaglabridins) are responsible for the yellow color of licorice. While the hispaglabridins A and B are antioxidants, glabridin and glabrene possess estrogen-like activity (Omar et al. 2012).

The active ingredient in licorice is glycyrrhizic acid, and together with its hydrolytic product, glycyrrhetinic acid, which is a 200–1,000 times more potent inhibitor of 11-ß-hydroxysteroid dehydrogenase 2 than glycyrrhizic acid itself, have well-known mineralocorticoid activity (Ruiz-Granados et al. 2012). The inhibition of 11-ß-hydroxysteroid dehydrogenase 2 prevents the physiological conversion of cortisol (which has activity at the mineralocorticoid receptor) to cortisone (which does not), and therefore results in excessive systemic cortisol levels (Fig. 15.4).

This can lead to a syndrome known as "apparent mineralocorticoid excess." Mineralocorticoids bind to the mineralocorticoid receptor of the principal cells of the distal nephron, where they translocate to the nucleus and initiate mRNA transcription and translation of so-called aldosterone-induced proteins. These proteins include luminal Na^+ channels known as epithelial, sodium channels (ENaC) (which are synthesized, redistributed from the cytosol to the luminal membrane and activated), and Na^+/K^+-ATPase (which is also synthesized, redistributed from the cytosol but to the basolateral membrane and then activated). Na^+ is more readily absorbed luminally by the ENaC channel, and extruded by the Na^+/K^+-ATPase, i.e., transepithelial Na^+-transport is enhanced. K^+ is transported in the opposite direction via the renal outer medullary potassium channel (ROMK), and H_2O as well as Cl^- follow Na^+, i.e., Na^+ and H_2O are absorbed, and K^+ is depleted (Bhalla and Hallows 2008; Wang 2006; Hebert et al. 2005) (Fig. 15.5). Licorice in quantities of as little as 50 g/day may cause mineralocorticoid-

induced hypertension (resulting from Na^+ and H_2O retention) and arrhythmias (e.g., ventricular fibrillation, due to severe hypokalemia). A combination of high dietary NaCl intake in salted licorice can therefore result in significant systemic hypertension.

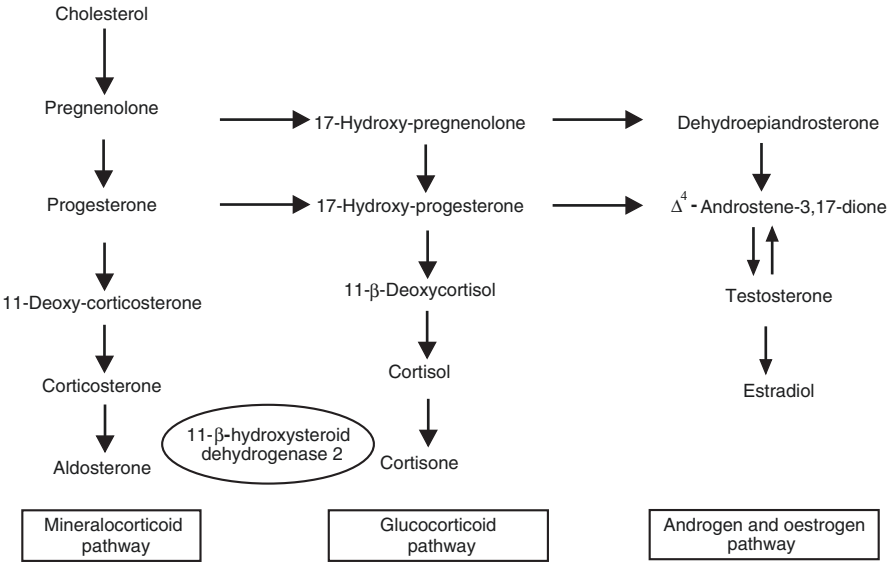

Fig. 15.4 Schematic representation of adrenocortical hormone biosynthesis pathways

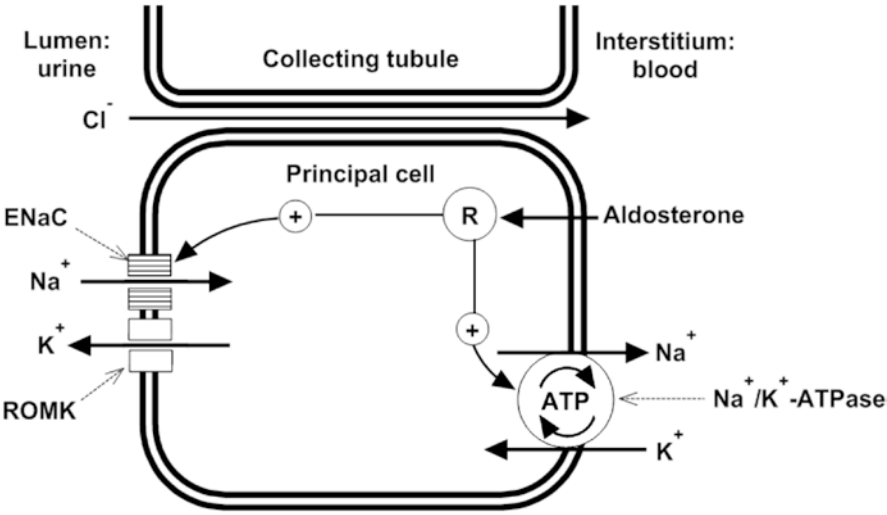

Fig. 15.5 Aldosterone-effects in the principal cells of the distal nephron. Mineralocorticoid receptor (*R*); epithelial sodium channel (*ENaC*); renal outer medullary potassium channel (*ROMK*); adenosine triphosphate (*ATP*)

Herb-Allopathic Drug Interactions and Cardiovascular Toxicity

A selection of plants for which clinically significant interactions with allopathic drugs have been documented, are discussed below.

Hypericum perforatum *(St. John's wort)*

This is a plant, the flowers and leaves of which are used primarily for mild to moderate depression and some of its symptoms, e.g., fatigue, anorexia, and insomnia. It has been used for a plethora of other conditions including coryza, herpes infections, and acquired immunodeficiency syndrome (AIDS) (Tachjian et al. 2010). *Hypericum perforatum* is indigenous to Europe, but is also found in southern and eastern Europe and parts of Asia.

St. John's wort is an inducer of the hepatic, drug-metabolising cytochrome P450 enzyme system, particularly CYP1A2, CYP3A4, but also CYP2C19 (Moses and McGuire 2010). CYP3A4 is involved in the metabolism of many allopathic drugs, including cardiovascular therapies, and St. John's wort should be avoided by patients using the prodrug clopidogrel, which is metabolized by both CYP3A4 and CYP2C19 systems. The concomitant use of clopidogrel (a $P2Y_{12}$ inhibitor) and the herbal product has been proven to decrease thrombocyte aggregation, which may lead to a risk of excessive bleeding (Lau et al. 2011).

When warfarin and St. John's wort are co-ingested, prothrombin times can be reduced and suboptimal anticoagulation may lead to a higher thromboembolic risk. This can be devastating, for example in those with metallic cardiac prostheses or atrial fibrillation on oral anticoagulation with a coumarin, and such patients should avoid this herbal product (Cohen and Ernst 2010). The concomitant intake of statins (HMG-CoA reductase inhibitors) and St. John's wort is not recommended, since the latter lowers statin blood concentrations, resulting in elevated cholesterol levels that may translate into an increased risk for cardiovascular events. Although the relationship between St. John's wort and hypertension is not well understood, it can inhibit re-uptake of serotonin, which may lead to the potentially life-threatening serotonin syndrome (which includes severe hypertension) (Cohen and Ernst 2010).

St. John's wort can induce the extensively distributed and expressed P-glycoprotein (P-gp), also known as multi-drug resistance protein. This is an ATP-dependent membrane efflux pump with a broad substrate specificity that has a protective action by pumping nonphysiological compounds, including drugs, out of cells. This may result in lowered blood levels and decreased efficacy of e.g. digoxin, a drug excreted from cells by P-gp. There are also potential interactions with dabigatran and dronedarone (both drugs being substrates for P-gp) (University of Washington 2014; Mendell et al. 2013).

Ginko biloba *(ginko)*

Extracts from the leaves from this tree, native to China, are said to have memory-enhancing, cognition-improving, antioxidant, neuroprotective, and cardio- and cerebrovascular benefits (Chen et al. 2012). The major components of this popular remedy include flavonoids, terpenoids, and organic acids. To date, results from trials regarding ginko's therapeutic efficacy regarding its beneficial effects on cognition have been ambiguous (Tachjian et al. 2010).

Ginko extracts may interact with warfarin and aspirin and increase the risk of hemorrhage (Tachjian et al. 2010). In several case reports, the use of ginko products and warfarin resulted in the development of intracerebral hemorrhage. There has been a case report on the development of spontaneous hyphema when the herbal extract was taken together with aspirin. Fatal intracerebral bleeding has also been recorded with the combined use of ginko and ibuprofen (Chen et al. 2012).

Ginko extracts may induce CYP3A4, thus enhancing the oxidative metabolism of substrates of this enzyme (Lau et al. 2011). This interaction may relate to the reduced efficacy of nicardipine, a Ca^{2+}-channel antagonist (Tachjian et al. 2010).

Allium sativum *(garlic)*

Garlic is an herb from the onion genus, which is native to central Asia and has been used for thousands of years for culinary and medicinal purposes. It has been widely used for treating infections because of its reputed antimicrobial and immunostimulatory effects (Tachjian et al. 2010). This herbal supplement is also commonly taken by persons with AIDS in the belief that it can bolster their immune response. It may have hypocholesterolemic, antihypertensive, and other anti-atherosclerotic effects; however, one clinical study showed no significant effects on low-density lipoprotein cholesterol or other plasma lipid levels (Tachjian et al. 2010). *Ajoene*, an unsaturated disulfide compound isolated from garlic does, however, inhibit collagen-induced platelet aggregation. Other organosulphur constituents in garlic have also exhibited inhibitory effects on human platelet aggregation both *in vitro* and *in vivo* (Chen et al. 2012).

Because the risk of bleeding is increased in anticoagulated patients or those on antiplatelet therapy, the concurrent use of garlic should be avoided. In cases where patients have been taking garlic-containing supplements, cessation is recommended before elective surgical procedures, particularly when anticoagulants (e.g., warfarin) or antiplatelet agents (e.g., aspirin) are consumed.

Panax ginseng *(ginseng)*

This plant is found in North America and in eastern Asia. The roots – and sometimes the leaves – have been used in folk medicine for many centuries, and the various extraction methods employed allow for a wide variation in the product composition. Immunostimulant, aphrodisiac, and antidiabetic properties as well as longevity have been attributed to these extracts (Tachjian et al. 2010). Other uses of ginseng are for its purported antihypertensive, hypolipidaemic, cognition-enhancing, anti-ulcerogenic, and anti-cancer effects (Chen et al. 2012). Its major constituents include ginsenosides, sterols, flavonoids, peptides, vitamins, polyacetylenes, minerals, β-elemine and choline.

Ginseng lowers blood pressure, apparently via effects on nitric oxide synthesis. Paradoxical hypertension, as well as psychomotor stimulation may occur, and caution is advised against its use in systemic hypertension (Lee et al. 2012). A nephrotoxic compound (germanium) in the extract is harmful to the ascending loop of Henle, antagonizing the action of loop diuretics. Ginseng extract, when co-administered with warfarin, has been reported to reduce prothrombin time (Tachjian et al. 2010; Izzo and Ernst 2009). Siberian ginseng interferes with the assay for digoxin levels, leading to false elevation in therapeutic drug monitoring levels (Tachjian et al. 2010).

Diagnosis and Management of Toxicity

It is challenging to establish the diagnosis of herbal poisoning or herb-allopathic drug interactions, because patients are often ill informed and view herbal products as safe, natural entities that are irrelevant to their conventional medical care, consequently omitting their mention in the anamnesis (Spoerke et al. 1987; Tachjian et al. 2010; Cohen and Ernst 2010). Diagnosing herbal toxicity primarily relies on a history of ingestion of cardiotoxic plant material and/or a suspicion generated by manifestations of direct toxicity, e.g., cardiac arrhythmias or inefficacy of allopathic drugs despite a reasonable certainty of compliance. Obtaining details of the constituents of many traditional medicines may be difficult, since they are often tightly guarded secrets not shared with patients or third parties (Van der Bijl and Van der Bijl 2012). Laboratory analyses for cardiac glycosides are available, and an immunoassay developed for the detection of digoxin also cross-reacts with other cardiac glycosides, such as oleandrin. However, more specific tissue and biological fluid assays for oleandrin have been developed (Poppenga 2010). The plasma level is not always a reliable indicator of toxicity, since it is only an indirect reflection of the myocardial tissue level (the true determinant of cardiac toxicity). An extreme

example hereof is cardiac amyloidosis, where glycosides are concentrated in the myocardium (bound directly to myocardial fibres), leading to toxicity at therapeutic plasma levels (Lawler et al. 2014). Other compounds and their metabolites can sometimes be identified in plasma and urine samples by chromatography and mass spectrometry (e.g., aconitine), but this is limited by availability of these techniques, and is complicated by the fact that the toxidrome might be caused by a mixture of compounds present in a herbal remedy (Goldfrank et al. 2006).

The management of plant-intoxicated patients includes measures common to all clinical toxicology, i.e., immediate discontinuation of further exposure to the herbal products, general resuscitative and life-support measures such as the administration of activated charcoal, gastric lavage (caveat: within 1 h of ingestion) as well as electrocardiographic and other (e.g. hemodynamic) monitoring methods for arrhythmias and other signs of cardiorespiratory compromise.

Specific antidotes for toxidromes caused by plants are non-existent, but digoxin-specific antibody fragments appear to cross-react with at least some other cardiac glycosides, and therefore have a potential application in the treatment of poisoning in humans with the latter phytochemicals (Bandara et al. 2010). These antibody fragments have a much higher affinity for glycosides than the Na^+/K^+-ATPase exchanger, and to chemical concentration gradient is created that allows the antibody fragments to bind much of the extracellular glycoside. The antibody fragment-glycoside complex is then excreted renally. The antibody fragments are supplied in powder form that has to be reconstituted with sterile water before intravenous injection. They may be administered *ex juvantibus* when a patient with suspected glycoside toxicity is *in extremis*, especially when it is uncertain whether a plasma assay will detect the compound in question. The effect of this antidote is usually seen within 30 min, but it might take longer (up to 4 h) to have the desired effect. Therapeutic drug monitoring is inaccurate in the first 3 weeks after administration of this antidote, since most assays measure both the free and antibody fragment-bound glycoside. Even though these antibodies are polyclonal, they have been safely administered to the same individuals on more than one occasion (Hauptman and Kelly 1999). Charcoal hemoperfusion has also been used to remove toxins, e.g., aconitine, but data are mostly limited to case reports (Lin et al. 2004; Fatovich 1992).

Arrhythmias may be treated with the complete armamentarium available to cardiac rhythm disturbances generally, i.e., temporary, transvenous pacing, overdrive pacing, antiarrhythmic drugs (e.g., phenytoin in glycoside toxicity – it may reverse heart block, possibly via a central mechanism), electrical cardioversion and defibrillation – as deemed appropriate to the specific rhythm disturbance in question. Hypotension can be treated with intravenous fluid (such as crystalloids) and/or vasopressors (such as phenylephrine), while hypertension can be managed with antihypertensive drugs (e.g., intravenous nitroprusside). There have been case reports (e.g., in aconitine toxicity) where persistent hypotension was treated with mechanical techniques, e.g., percutaneous cardiopulmonary bypass, extracorporeal membrane oxygenation, and ventricular assist devices (Fatovich 1992; Lin et al. 2004). Acute coronary syndromes should be treated by means of standard protocols,

although when these are cocaine-induced, β-adrenoreceptor-antagonists should be avoided (which will allow unopposed, α-adrenoreceptor-mediated vasoconstriction) and phentolamine (an α-adrenoreceptor-antagonist) can be administered therapeutically (Lange et al. 1989).

Treatment of the cardiovascular manifestations of plant toxicity is mostly not evidence-based. The old adage that prevention (including education) is better than cure, is particularly applicable to this scenario.

Conclusions

There is a conspicuous lack of scientific data pertaining to the efficacy and safety of herbal products. Currently, randomized, controlled clinical trials are not required by regulatory agencies, nor demanded by consumers and healthcare practitioners alike before marketing. Many thousands of these products, often labelled as dietary supplements, are sold worldwide, and consumers are under the impression that they are natural and safe. Only when herbal remedies have caused serious harm do regulatory agencies act, as demonstrated by the banning of ephedra by the Food and Drug Administration in the U.S. in 2004. Rather than waiting for adverse effects to occur, it is the opinion of the authors that manufacturers of herbal products should be compelled by law to prove that their products are efficacious and safe. Biological variability (geographical location, climate and soil conditions, etc.), manufacturing and storage techniques, contamination (pesticides, metals, intentional and unintentional adulteration with allopathic drugs), and general lack of consistency in the quality of these herbal products are of great concern. Furthermore, aggressive marketing techniques, in which bold as well as unsubstantiated claims for products are frequently made, are being used by manufacturers.

All healthcare practitioners, especially cardiologists, should be aware of the potential dangers, in the form of either the direct toxicity or drug-herb interactions that these herbal products pose. To this end, probing questions must be asked (patients anticipate doctors' disapproval when they report using alternative remedies) during the anamnesis regarding the use of these products, and a high index of suspicion should be maintained whenever patients present with unexplained symptoms/toxidromes or atypical responses to allopathic medicines.

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