G Model
PHYTOL 1300 No. of Pages 13
ARTICLE IN PRESS

Phytochemistry Letters xxx (2016) xxx–xxx

Contents lists available at ScienceDirect

Phytochemistry Letters

journal homepage: www.elsevier.com/locate/phytol

A window on cyclitols: Characterization and analytics of inositols

Hossam Al-Suod[a,b], Magdalena Ligor[a], Ileana-Andreea Raţiu[b,c], Katarzyna Rafińska[b], Ryszard Górecki[d], Bogusław Buszewski[a,b,*]

[a] Department of Environmental Chemistry and Bioanalytics, Faculty of Chemistry, Nicolaus Copernicus University,7 Gagarina Str., 87-100 Torun, Poland
[b] Interdisciplinary Centre of Modern Technologies, Nicolaus Copernicus University, 4 Wileńska Str., 87-100 Torun, Poland
[c] Faculty of Environmental Science and Engineering, Babeş Bolyai University, Str. Fântânele nr. 30, 400294 Cluj-Napoca, Romania
[d] Department of Plant Physiology and Biotechnology, Faculty of Biology and Biotechnology, University of Warmia and Mazury, Oczapowskiego 1A, PL-10-719 Olsztyn, Poland

ARTICLE INFO

Article history:
Received 30 September 2016
Received in revised form 23 November 2016
Accepted 6 December 2016
Available online xxx

Keywords:
Cyclitols
myo-inositol
D-pinitol
Extraction methods
Analytical methods

ABSTRACT

Cyclitols are cycloalkanes with one hydroxyl group on each of three or more ring atoms, also called cycloalkane polyols or sugar alcohol which attract attention since they have numerous pharmaceutical properties and are widespread in the plants. Inositols are important cyclitols, which constitute a group of naturally occurring polyhydric alcohols and some isomers of this group can be commonly found in most plants, provided adequate methods of detection are employed. This review presents plant containing cyclitols, with emphasis put on their pharmaceutical properties. The text focuses on sample preparation, extraction and purification and on analysis of cyclitols in plants. In addition, it addresses the application of different methodologies utilized in the analysis of cyclitol compounds in plant.

1. Introduction

Cyclitols are cycloalkanes with one hydroxyl group on each of three or more ring atoms, hence they are also called cycloalkane polyols or sugar alcohol. Cyclitols attract attention since they are widely distributed in the plant kingdom and other living cells and display a broad range of biological activities. They play a particularly important role in cell functioning because they are involved in signal transduction, membrane biogenesis, cell wall formation, ion channel physiology, phosphate storage, osmoregulation, and show anti-oxidation activity (Bieleski, 1994; Donahue et al., 2010; Loewus and Murthy, 2000; Merchant et al., 2006).They are also one of the compatible solutes which are formed in a plant as a response to salt or water stress (Arndt et al., 2004; Das-Chatterjee et al., 2006; Merchant et al., 2006).

Inositols are the most widespread cyclitols in eucaryotic cells, with empirical formula $C_6H_{12}O_6$ (1,2,3,4,5,6-cyclohexaneol). These chemical compounds exist in nine possible stereoisomers. Five of them, *myo*-, *scyllo*-, *muco*-, neoand D-*chiro*-inositol occur naturally, while the other four possible isomers (L-*chiro*-, *allo*-, *epi*-, and *cis*-inositol) are derived from *myo*-inositol (Campbell et al., 2011; Loewus and Murthy, 2000). Among all the known isomers, *myo*-inositol is the most ubiquitous in nature (Campbell et al., 2011; Larner, 2002). This compound is present in all eukaryotic cells where there is a structural basis for a number of secondary messengers. It is also an important component of structural lipids (phosphatidylinositol (PI) and their various phosphates, the phosphatidylinositol phosphate (PIP) lipids. Some of inositols are commonly found in nature either as pure compounds or as their derivatives (Lee and Morris, 1963; Phillips et al., 1982; Sanz et al., 2008).

Some of the methyl ether derivatives of inositol are plant secondary metabolites, compounds that are not directly involved in the normal growth but which play an important role in the defense against unfavorable environmental conditions. Among them we can distinguish 5-*O*-methyl-*myo*-inositol (sequoyitol), 1-*O*-methyl-*myo*-inositol (bornesitol), 4-*O*-methyl-*myo*-inositol (ononitol), 5-*O*-methyl-allo-inositol (brahol), di-*O*-methyl-(+)-chiro-inositol (pinpollitol) and 1L-2-*O*-methyl-*chiro*-inositol (L-quebrachitol) (Ahmad et al., 1998; Endringer et al., 2009; Gallagher, 1975; Negishi et al., 2015; Schilling, 1976). Sequoyitol has been found in leaves of ginkgo (Negishi et al., 2015) while bornesitol has been found in plants from the Gentianaceae as well as Menyanthacea and Apocynaceae families (Endringer et al., 2009; Schilling, 1976). Ononitol is produced by *Medicago sativa* (Horbowicz et al., 1995; McComb and Rendig, 1962), nodules of

* Corresponding author at: Department of Environmental Chemistry and Bioanalytics, Faculty of Chemistry, Interdisciplinary Centre of Modern Technologies, Nicolaus Copernicus University, 7 Gagarina Str., 87-100 Torun, Poland.
E-mail address: bbusz@chem.umk.pl (B. Buszewski).

http://dx.doi.org/10.1016/j.phytol.2016.12.009

Pisum sativum and *Glycine max* (Streeter, 1985). Barahol has been extracted from *stocksia brahuica* while pinpollitol from *pinus radiata* (Ahmad et al., 1998; Gallagher, 1975). L-quebrachitol can be obtained from *Hevea brasiliensis* latex in the process of rubber tapping (Alphen, 1951) and from *Allophylus edulis* (Díaz et al., 2008).

3-*O*-Methyl-D-*chiro*-inositol called D-pinitol is the most widely distributed inositol ether in plants, with its two enantiomers present in various plant sources. It was first isolated in the sugar pine (*Pinus Lambertiana*) (Anderson et al., 1952). D-pinitol is a naturally occurring compound present in peanut (Lee and Morris, 1963), *Bougainvillea spectabilis* (Jawla et al., 2013; Narayanan et al., 1987; Vidhate et al., 2015), and *Argyrolobium roseum* (Ram et al., 2007; Sharma et al., 2016), but for manufacturing purposes it is generally extracted from soybean (Kawai and Kumazawa, 1982; Phillips et al., 1982; Streeter et al., 2001) and also from carob (Baumgartner et al., 1986; Cháfer and Berna, 2014; Tetik and Yüksel, 2014).

2. Nomenclature of *myo*-inositol and *chiro*-inositol

Myo-inositol is a symmetrical compound, which is divided into mirror image halves along the plane of symmetry between C2 and C5. In the case of free *myo*-inositol without any substituent, numbering carbon atoms in counter-clockwise (D-*myo*-inositol) or clockwise direction (L-*myo*-inositol) represents the same compound called *myo*-inositol. When a hydroxyl group is substituted by another substituent (phosphate, *O*-methyl or other groups) at prochiral position, asymmetry is created. Then the configuration follows D or L designation with lowest-numbered chiral atom representing the substituent. *Chiro*-inositol is an asymmetrical compound with two enantiomers, D-*chiro*-inositol and L-*chiro*-inositol. The carbons of D-*chiro*-inositol ring are numbered counter-clockwise, while L-*chiro*-inositol is numbered clockwise (see Table 1, which illustrates common cyclitols found in plants, with their structures and physical and chemical properties).

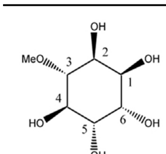
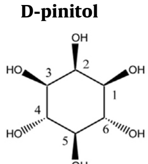
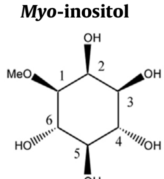
3. Pharmacological applications of cyclitols

Besides their important biological functions in plants, cyclitols have many pharmaceutical properties which are particularly important from medical point of view. Recently many studies have focused on the ability of *myo*-inositol and D-*chiro*-inositol to act as novel insulin-sensitizing drug to enhance ovulation rate or improve fertility in women with the polycystic ovary syndrome (PCOS) (Cheang et al., 2008; Costantino et al., 2009; Nestler et al., 1999; Papaleo et al., 2007). Other clinical studies in human patients have also reported that *myo*-inositol is effective in treatment of psychiatric dysfunctions such as panic attacks (Benjamin et al., 1995), depression (Levine et al., 1995), obsessive–compulsive disorder (OCD) (Fux et al., 1996) and premenstrual dysphoric disorder (PMDD) (Gianfranco et al., 2011). Moreover, Phytic acid (InsP6 or IP6) and Ins(1,2,3)P3 are inositol-derivatives that are present in substantial amounts in almost all plant and mammalian cells. They have multiple biological functions, acting as anticancer and antioxidant agents (Mansell et al., 2010; Phillippy and Graf, 1997; Shamsuddin et al., 1996; Yusoff et al., 2011). Inositol 1,4,5-trisphosphate (IP3) and inositol 1,3,4,5-tetrakisphosphate (IP4) are critical second messengers which regulate calcium (Ca^{2+}) homeostasis (Soriano and Banting, 1997).

Many recent studies indicate that also D-pinitol, 3-*O*-methyl ether of D-*chiro*-inositol, has a broad spectrum of pharmacological applications. It has been found in plants from Pinacae and Leguminosae family. Soybean also has particularly high D-pinitol content, which constitutes about 1% of dry weight of soybean meal. This compound was shown to possess insulin-like properties and it can be useful in treating diabetes by reducing the level of blood glucose in mice (Bates et al., 2000), in rats (Kim et al., 2005) and in humans (Hernández-Mijares et al., 2013).

Sivakumar and Subramanian (2009) reported that D-pinitol can act as anti-oxidant agent which protects the pancreatic tissue of rats from free radical-mediated oxidative stress in addition to its anti-diabetic property. Moreover, it is an effective blocker of the NF-$_{k}$B pathway, and it also shows potential in treatment of NF-$_{k}$B

Table 1
Common cyclitols distributed in plants.

Cyclitols	CAS No.	M. F	M. W	Amounts in different plants (mg/g)	M. P °C	logP	Density g/cm^3	Optical rotation	Ref.
 **D-pinitol**	10284–63-6	$C_7H_{14}O_6$	194.18	sticky mouse-ear (2.6) chickweed (2.75) *Glycine max* (0.55)	179–185	−3.18050	1.56	$[\alpha]_D^{20}$ +65 (c 0.4, H_2O)	Calle et al. (1986), Negishi et al. (2015), Streeter (1985)
 ***Myo*-inositol**	87–89-8	$C_6H_{12}O_6$	180.16	*Glycine max* (0.90)	225–227	−3.83460	1.72	In active	Dittrich and Danböck (1976), Streeter (1985)
 **L-bornesitol**	–	$C_7H_{14}O_6$	194.18	*Lathyrus odoratus* L. Petal: 2.9 Flower: 5.0 Stem: 1.1 Leaf: 3.7	201–202	−3.18050	1.72	$[\alpha]_D$ +30.6 (c 0.8, H_2O)	Ichimura et al. (1999)

Please cite this article in press as: H. Al-Suod, et al., A window on cyclitols: Characterization and analytics of inositols, Phytochem. Lett. (2016), http://dx.doi.org/10.1016/j.phytol.2016.12.009