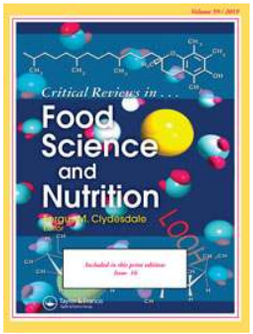

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Pharmacological potential of methylxanthines: Retrospective analysis and future expectations

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ABSTRACT

Methylated xanthines (methylxanthines) are available from a significant number of different botanical species. They are ordinarily included in daily diet, in many extremely common beverages and foods. Caffeine, theophylline and theobromine are the main methylxanthines available from natural sources. The supposedly relatively low toxicity of methylxanthines, combined with the many beneficial effects that have been attributed to these compounds through time, generated a justified attention and a very prolific ground for dedicated scientific reports. Methylxanthines have been widely used as therapeutical tools, in an intriguing range of medicinal scopes. In fact, methylxanthines have been/were medically used as Central Nervous System stimulants, bronchodilators, coronary dilators, diuretics and anti-cancer adjuvant treatments. Other than these applications, methylxanthines have also been hinted to hold other beneficial health effects, namely regarding neurodegenerative diseases, cardioprotection, diabetes and fertility. However, it seems now consensual that toxicity concerns related to methylxanthine consumption and/or therapeutic use should not be dismissed. Taking all the knowledge and expectations on the potential of methylxanthines into account, we propose a systematic look at the past and future of methylxanthine pharmacologic applications, discussing all the promise and anticipating possible constraints. Anyways, methylxanthines will still substantiate considerable meaningful research and discussion for years to come.

KEYWORDS

Caffeine; diabetes; methylxanthine; neurodegenerative diseases; theobromine; theophylline

1. Introduction

There are compelling historical and anthropological evidences of methylxanthines being included in human diet for a very long time. Nowadays, the consumption of products containing methylxanthines is undeniably widespread and very common in human populations. And other than the more traditional dietary sources of methylxanthines, like coffee, tea or chocolate, there are other methylxanthine-containing products that are gathering increased popularity, but also raising some concerns. That is the case of energetic drinks and food supplements, which often contain significantly increased amounts of methylxanthines with regard to the traditional sources. Caffeine is the more thoroughly studied methylxanthine so far, probably due to the high prevalence of its consumption in present diet. Methylxanthine therapeutic properties have been reported in a number of pathologic contexts. They have been used in medicine for decades in different medical scopes, namely respiratory disease (Lam and Newhouse 1990), cardiovascular disease (Batterman et al. 1959) and cancer (Hayashi et al. 2005; Kimura et al. 2009). However, the mechanisms underlying the beneficial action of methylxanthines in such conditions have not always been clarified.

Herein, we discuss the historical relevance of methylxanthine use in medicine and the emerging contexts where they have shown promise and were hinted as potential therapeutical tools. The current therapeutical uses in medicine are summarized in Fig. 1, and will be discussed in later sections. The molecular mechanisms involved in the beneficial effects of methylxanthines in various scopes will also be discussed.

2. Methylxanthine chemistry and analysis

Methylxanthines are heterocyclic organic compounds that are methylated derivatives of xanthine, therefore comprising coupled pyrimidinedione and imidazole rings (Talik, Krzek, and Ekiert 2012). Caffeine (1,3,7-trimethylxanthine), theophylline (1,3-dimethylxanthine) and theobromine (3,7-dimethylxanthine) are the methylxanthines most frequently available from natural sources (Fig. 2). They differ in the number (caffeine has three, the others two) and position of N-CH3 groups. Paraxanthine (1,7-dimethylxanthine), another relevant methylxanthine, is not produced by plants but appears as a product of caffeine metabolism, namely in humans (Nehlig 2015). Methylxanthines are present in nearly 100 species of 13 orders of the Plant Kingdom (Ashihara and Crozier 1999; Ashihara and Suzuki 2004), including tea (*Camellia sinensis L.*), coffee (*Coffea sp.*) and cacao (*Theobroma cacao L.*). Caffeine is present in *Coffea* species (0.4 to 2.4% dry weight (Mazzafera and Carvalho 1991)) and in the tea plants

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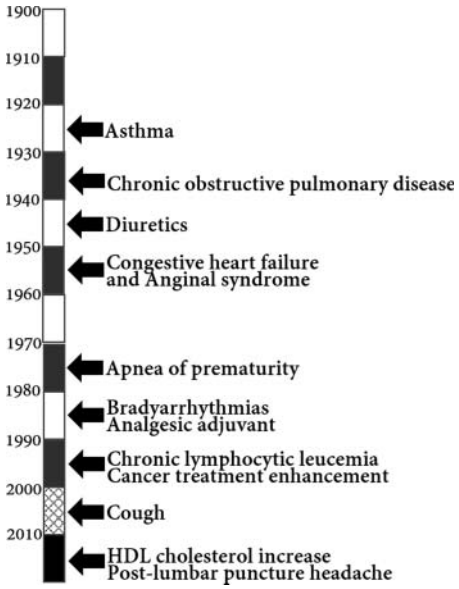
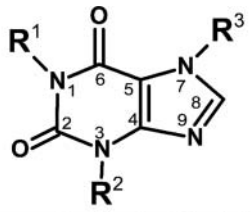


Figure 1. Chronology of methylxanthine medical use.

Camellia sinensis, Camellia assamica and *Camellia taliensis* (2–3%) (Ashihara, Sano, and Crozier 2008). Theobromine may be present in some *Camellia* species, although *Theobroma cacao* is normally reported as its major natural source (Ashihara, Sano, and Crozier 2008). Theophylline is abundant in tea species, but is also present in trace amounts in cocoa and coffee beans (Barnes 2013). *Paullinia sp*., *Cola sp*. and *Citrus sp*. also contain methylxanthines (Atawodi et al. 2007; Baumann, Schulthess, and Hänni 1995; Kretschmar and Baumann 1999; Weckerle, Stutz, and Baumann 2003). Regarding human consumption through dietary products, caffeine and theophylline (typically at much lower amounts) may be ingested in coffee, tea, cola beverages and chocolate (Stavric 1988a), although tea contains less caffeine than coffee (Gilbert et al. 1976). Tea and chocolate should account for most theobromine intake through diet (Stavric 1988c).

Methylxanthines have been proposed to have many systemic effects in humans. Nevertheless, the mechanisms by which methylxanthines exert their biological effects are not fully understood. Nonetheless, some studies tried to establish chemical structure-bioactivity relationships for methylxanthines, evaluating the extent of their interaction with particular molecular targets (see (Monteiro et al. 2016) for a detailed review). Classically there are four mechanisms of action proposed for methylxanthine



Name	R^1	R^2	R^3
Xanthine	H	H	H
Caffeine	CH_3	CH_3	CH_3
Theophylline	CH_3	CH_3	H
Theobromine	H	CH_3	CH_3
Paraxanthine	CH_3	H	CH_3

Figure 2. Chemical structures of natural methylxanthines.

physiological action. These are adenosine receptors antagonism, phosphodiesterase inhibition, modulation of the action of receptors and regulation of intracellular calcium levels through ryanodine channels (Chen and Chern 2011; Choi et al. 1988; Dent et al. 1994; Liu and Meissner 1997; McPherson et al. 1991; Tazzeo et al. 2012) (Table 1). Antagonism of adenosine receptors is thought to be the main mechanism of methylxanthine action, and their activity is thought to be exerted preferably by modulation of A_1 and A_{2A} receptors, which are inhibited in the μM range (Fredholm et al. 1999).

There are many available technical approaches to extract, identify and quantify these compounds in different kinds of samples (food, beverages and even biological fluids) and many of those techniques also aim the simultaneous determination of the main methylxanthines (caffeine, theobromine and theophylline) (Fig. 3). They commonly involve some kind of pre-treatment protocols to eliminate unwanted matrix interferences, usually involving liquid-liquid (Begas et al. 2007; Bendriss, Markoglou, and Wainer 2000; El-Yazigi et al. 1999; Krul and Hageman 1998; Newton et al. 1981b; Van Soeren et al. 1996) or solid-phase extraction (Emara 2004; Fenske 2006; Georga, Samanidou, and Papadoyannis 2000; Setchell et al. 1987; Srdjenovic et al. 2008). Methylxanthine extraction is usually based in sequential aqueous extraction, followed by organic extraction (with dimethyl chloride, chloroform, methanol or *n*-hexane (Belščak et al. 2009; Caudle, Gu, and Bell 2001; Hulbert et al. 1998; Unachukwu et al. 2010; Xia, Ni, and Kokot 2013)). Liquid chromatography (LC), namely reversed-phase high-performance liquid chromatography (RP-HPLC) has been the choice normally used for methylxanthine separation and determination. Low pressure chromatography was also recently proposed as an analytical alternative for methylxanthine separation and screening in samples (Santos and Rangel 2012). Methylxanthine identification and quantification is commonly spectrophotometrically performed (by DAD or UV, at or about 273 nm (Adams, Vandemark, and Schmidt 1976; Seeram et al. 2006)). HPLC coupled to mass spectrometry methods represent a more incisive recent resource, allowing acquiring structural information and unequivocal identification of the compounds (Bech and Bossi 2015; Huck, Guggenbichler, and Bonn 2005; Ptolemy et al. 2010).

3. Methylxanthine pharmacokinetics

Many beneficial physiological effects have been attributed to methylxanthines, and they have even established themselves as valid therapeutic tools in some contexts. These health and pharmacological effects should substantially depend on the bioavailability and biotransformation of methylxanthines in the organism. Therefore, a growing number of studies were made in order to determine pharmacokinetic parameters for every one of the main natural methylxanthines.

Methylxanthines (caffeine, theophylline, theobromine, and paraxanthine) are thought to distribute through all body fluids and to cross all biological membranes upon administration to both animals and humans. Nevertheless, after ingestion or administration, methylxanthines are not expected to accumulate in organs or tissues and, are posteriorly metabolized in the liver (Arnaud 2011).

A study aiming at determining pharmacokinetic parameters of caffeine, theophylline, theobromine and also paraxanthine in

Table 1. Main mechanisms of action of methylxanthines and available parameters suggesting physiological concentrations of interest.

Methylxanthine physiological mechanism	Methylxanthine	Effective concentrations (μM)	References
Antagonism of adenosine receptors[a]	*Caffeine*	*55 (A_1) and 50 (A_{2A})*	(*Daly et al. 1985*)
	Theophylline	*14*[a]	(*Daly et al. 1985*)
Phosphodiesterase inhibition[b]	*Caffeine*	*1000*	(*Butcher and Sutherland 1962*)
	Theophylline	*200-300*	(*Butcher and Sutherland 1962*)
	Theobromine	*1000*	(*Butcher and Sutherland 1962*)
GABA receptor modulation	*Caffeine*	*500*[b]	(Shi, Padgett, and Daly *2003*)
Activation of ryanodine-sensitive calcium channels[b]	*Caffeine*	*1760 or ≈6000*	(*Gaburjakova and Gaburjakova 2014*) (*McPherson et al. 1991*)

[a]*dissociation constant values;* [b]IC_{50}

the same individuals, for direct comparison purposes (Lelo et al. 1986) revealed that caffeine and paraxanthine on one hand, and theophylline and theobromine on the other, had similar pharmacokinetic profiles, namely concerning the calculated half-lives and respective plasma clearances. Caffeine and paraxanthine displayed shorter half-lives (4.1 and 3.1 h, respectively) comparatively to for theophylline and theobromine (6.2 and 7.2 h) and higher plasma clearances (2.07 and 2.20 mL $min^{-1}kg^{-1}$, respectively compared to 0.93 and 1.20 mL $min^{-1}kg^{-1}$, for theophylline and theobromine). Therefore, systemic effects of theophylline and theobromine, which remaining longer in the body, should be expected to be maintained for a longer period of time. As for the volume of distribution at steady state, theophylline had a lower value (0.44 L/kg^{-1}) as compared to the others (0.63 – 0.72 L/kg^{-1}).

Caffeine is rapidly and completely absorbed in humans at the gastrointestinal level, mainly at small intestine, but also at the stomach (20%) (Chvasta and Cooke 1971). Following a 5 mg/kg oral administration, plasma peak concentration was shown to be attained at 29.8 ± 8.1 min.kg, with a peak plasma concentration of 10.0 ± 1.0 μg/mL (Blanchard and Sawers 1983), a concentration that should raise limited action on caffeine molecular targets (<IC_{50}). However, a more recent study predicted a maximal plasma concentration of 1335 ng/ml after consumption of one

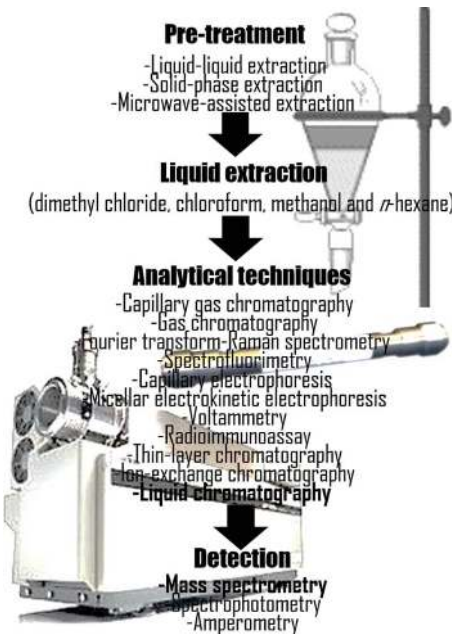


Figure 3. General methods for methylxanthine analysis.

cup of coffee (about 80 mg of caffeine), for which expected systemic effect should be even lower (Zandvliet et al. 2005). Other studies reported maximum concentrations in the same range after caffeine intake of about 100 mg (Perera, Gross, and McLachlan 2010; Teekachunhatean et al. 2013). Interestingly, administration route does not significantly change these parameters in the case of intravenous administration (Blanchard and Sawers 1983; Newton et al. 1981a). However, enema exposure lowers relative bioavailability of caffeine by about 3.5 times with regard to oral consumption (Teekachunhatean et al. 2013) while inhalation lowers it to 60% (Zandvliet et al. 2005). These studies show that caffeine bioavailability is dependent of the administration route and thus, it should be taken in consideration when discussing its pharmacological potential. Moreover, studies suggested that the rate of consumption, as well as the temperature of beverage and vehicle (coffee versus energy drink), had little impact on caffeine pharmacokinetics (White et al. 2016) illustrating that the stability of the compound is independent of those factors. Caffeine first pass effect (concentration reduction before reaching systemic circulation) is thought to be minimal (Yesair, Branfman, and Callahan 1984) and elimination was proposed to be a first-order process (Arnaud 1993; Newton et al. 1981a) and is described by a one-compartment open model system in the dose range of intake of 2 – 10 mg/kg (Blanchard and Sawers 1983; Bonati et al. 1982; Newton et al. 1981a). Another study proposed linear pharmacokinetics for caffeine in intakes between 70 and 100 mg (about a cup of coffee), while for higher doses (between 250 and 500 mg) the kinetics were non-linear and half-life was prolonged, what could insinuate prolonged systemic/pharmacological effects (Kaplan et al. 1997). Interindividual significant variations in caffeine half-lives (2.3 – 9.9 h) should indicate idiosyncratic factors determining elimination (Blanchard and Sawers 1983). For instance, the elimination of methylxanthines (namely caffeine and theophylline) was proposed as being considerably slower in the neonate, with caffeine being excreted in the urine of newborns mainly unchanged (85%, while 2% in adults) (Aranda, Turmen, and Sasyniuk 1980). This suggests that fetal and neonatal exposure could increase the susceptibility to caffeine systemic effects, and this concern will in fact be addressed in a later section of this review.

As for caffeine, theophylline is also rapidly and completely absorbed (Hendeles and Weinberger 1983; Ogilvie 1978; Yesair, Branfman, and Callahan 1984), with the major part of the absorption taking place before the jejunum (Brouwers et al. 2005). Absorption of theophylline was proposed to follow first-order kinetics, at least following oral administration in the 125 – 500 mg range (Rovei, Chanoine, and Strolin Benedetti 1982).

Accumulation of theophylline in brain, liver, muscle, and adipose tissue is lower than that of caffeine (Ståhle 1991), probably reflecting its lower lipophilicity. Theophylline pharmacokinetics were accessed in asthmatic patients, with reported peak plasma concentration of 8.4 ± 1.7 mg/L, attained at 2.2 ± 0.8 h after oral ingestion of a 5 mg/kg dose (Becker et al. 1984). Other authors reported peak plasma theophylline levels of 7 mg/L after a single oral dose of 250 mg (French and Mildon 1979). Within therapeutic range plasma levels, first-order kinetics are assumed to apply to theophylline and, thus, a one-compartment model or a model-independent approach is routinely used for dose adjustments (Butts, Secrest, and Berger 1991). However, theophylline frequently exhibits nonlinear pharmacokinetics, as suggested from studies in animal models (El-Yazigi and Sawchukx 1981; Teunissen et al. 1985), young children (Ginchansky and Weinberger 1977; Sarrazin et al. 1980; Weinberger and Ginchansky 1977), and patients treated for obstructive pulmonary diseases (Butts, Secrest, and Berger 1991). Interindividual variability also seems to occur regarding theophylline clearance (Fleetham et al. 1981), which was suggested to be influenced by age, sex, diet, liver function, and also external influences such as smoking (French and Mildon 1979; Ogilvie 1978). This is why the recommended standard pharmacological doses should be seen as mere guidelines and approximations, and physicians could begin by prescribing smaller doses and warily increase from there at tolerated intervals (Ogilvie 1978).

Theobromine pharmacokinetics have not been subject of as many reports as the other main natural methylxanthines. Anyway, it is interesting that the absorption when ingested in chocolate (80%) is lower than when ingested in a solution, what is thought to be related with interaction with other chocolate components (Shively et al. 1985). Theobromine was found in all fluids (including plasma, saliva, and breast milk) 2–3 h after ingestion of an oral dose of chocolate containing 240 mg by nursing mothers, with concentrations peaking from 3.7 to 8.2 mg/L (Resman, Blumenthal, and Jusko 1977). Another study reported that an oral dose of chocolate containing 370 mg of theobromine produced a plasma peak concentration of 8.05 μg/mL after 2 h (Mumford et al. 1996). Another reported peak plasma value of 9.8 ± 0.8 mg/L, occurred 2.1 ± 0.6 hours after drug ingestion (Simons et al. 1985). Studies reported theobromine half-lives of 7.1 ± 2.1 h (a dose of 240 mg of theobromine in nursing mothers) (Resman, Blumenthal, and Jusko 1977), 6.1 ± 0.7 h (after a single oral dose of 6 mg/kg normal male volunteers) (Drouillard, Vesell, and Dvorchik 1978), 9.28 ± 0.7 h (10 mg/kg theobromine in healthy, nonsmoking men) (Tarka et al. 1983), and 5.5 ± 1,8 h (10 mg/kg dose in young patients with asthma) (Simons et al. 1985). These relatively high half-life values (comparing to caffeine, for instance) should imply greater duration of action and longer intervals between doses. Theobromine clearance was proposed to follow first-order kinetics with a one-compartment open model (Tarka et al. 1983).

Methylxanthines are mainly metabolized in the liver (Arnaud 2011). Several demethylation processes may represent the first steps in the metabolism of caffeine (Stavric 1988a), as shown in Fig. 4. Caffeine is primarily metabolised via oxidative demethylation by liver cytochrome P450 1A2 (CYP1A2) (Kot and Daniel 2008), and only less than 2% of the ingested caffeine is excreted in human urine (Arnaud 2011). Caffeine may be in fact demethylated onto paraxanthine (84%), theobromine (12%) or theophylline (Nehlig 2015). These are further metabolized and then excreted in the urine. The major caffeine-derived metabolites found in urine are paraxanthine, 1-methylxanthine, 1,7-dimethyluric acid, 1-methyluric acid, and 5-acetylamino-6-formylamino-3-methyluracil (Begas et al. 2007). Urinary excretion of methylated xanthines and uric acids was shown to take place within 24 hours upon coffee consumption, proving the rather fast metabolism of caffeine in humans (Martínez-López et al. 2014). Interindividual differences in caffeine metabolism are explained by CYP1A2 polymorphisms (Grosso and Bracken 2005), and should determine differences in pharmacologic responses to caffeine. The other major enzymes involved in caffeine metabolism are N-acetyltransferase and xanthine oxidase (Fenster et al. 1998). As for theophylline, it mainly undergoes 8-hydroxylation to 1,3, dimethyluric acid (around 60–80%). N-demethylation to 1-methylxanthine (8–24%) or to 3-methylxanthine (5–15%) being alternative routes (Fuhr et al. 1993). For theobromine N3-demethylation accounted for 58 ± 7% and N7-demethylation for 27 ± 6%, of its urinary metabolites (Rodopoulos, Höjvall, and Norman 1996). These studies highlight that pharmacologic responses to methylxanthines are highly dependent of several factors that must be taken in consideration, particularly idiosyncrasies that may impact individual response, which depends on methylxanthine metabolism, excretion and bioavailability.

A second mechanism proposed to account for methylxanthine physiologic activity is the inhibition of phosphodiesterases (Beavo et al. 1970; Choi et al. 1988; Herman and Herman 2013), phosphodiesterase-4 (PDE4) in particular (Ruangkittisakul and

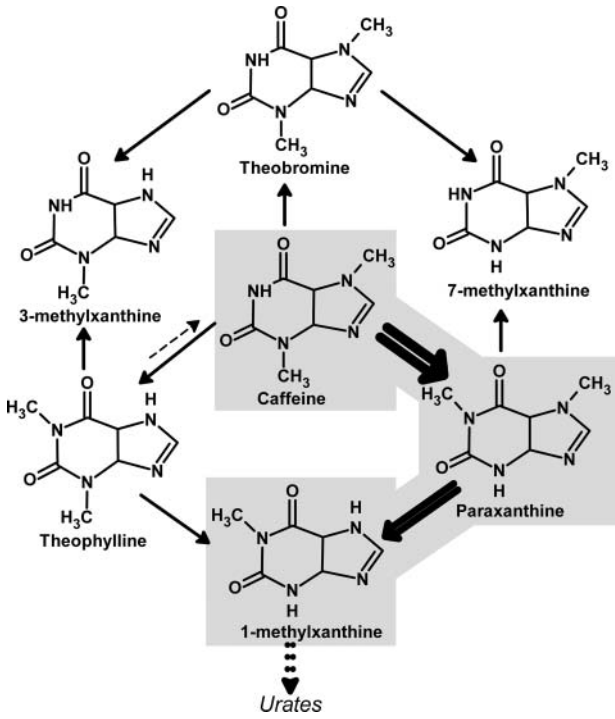


Figure 4. Demethylation processes that occur as the first steps in the metabolism of caffeine (mostly metabolized to paraxanthine, shadowed path), and that originate other methylxanthines (thicker arrows, and in this case mean predominant routes). Further metabolism involves oxidation to urates (Stavric 1988a).

Ballanyi 2010; Sugimoto et al. 2014), halting the degradation and therefore promoting cAMP concentration increase. Naturally occurring methylxanthines are all considered relatively weak competitive inhibitors of phosphodiesterases (Daly 2007), but theophylline has a more potent action than caffeine (and theobromine) at this level (Stavric 1988a).

Another mechanism proposed to elicit methylxanthine mechanistic activity concerns the modulation of GABA receptors. In fact, caffeine (Lopez et al. 1989) and theophylline (Sugimoto et al. 2001) were reported to modulate the ion transport accomplished by these structures. Caffeine and theophylline should act as antagonists or reverse agonists at benzodiazepine sites, while also interacting with the picrotoxinin and GABA sites (Roca, Schiller and, Farb 1988; Shi, Padgett, and Daly 2003).

The other mechanism classically related to methylxanthine action is the stimulation of calcium release from intracellular stores through ryanodine-sensitive calcium channels located in the sarcoplasmic reticulum (Daly 2000; Gaburjakova and Gaburjakova 2014; McPherson et al. 1991; Müller and Daly 1993; Rousseau et al. 1988). Caffeine is a full agonist of the ryanodine receptors, prompting Ca^{2+} transient fluxes (Kuemmerle et al. 1994; Shi, Padgett, and Daly 2003; Shou et al. 2013), while theophylline and theobromine are less effective in increasing intracellular calcium elevation through this mechanism (Müller and Daly 1993). This mechanism may be in the genesis of caffeine's pro-arrhythmic action, since it was suggested that it may result from a caffeine-dependent shift in cardiac ryanodine receptors luminal Ca^{2+} activation threshold (Kong et al. 2008). Activation of ryanodine receptors by caffeine may also contribute to its beneficial effects in cancer contexts (Mariot et al. 2000), but it should be kept in mind that it only occurs at significantly high concentrations, at least *in vitro*.

Of these mechanisms proposed for the action of methylxanthines, adenosine receptor antagonism should be the more relevant (Daly 2007; Fredholm 1985; Fredholm et al. 1999), since physiological plasma concentrations achieved by dietary intake ($<100\mu$M) should not be effective in interfering with the activity of phosphodiesterases and $GABA_A$ receptors, or ryanodine receptors (Daly 2007; Fredholm et al. 1999; Marangos et al. 1979) (Table 1). Pharmacological doses (in mM concentration range) may indeed prompt the inhibition of phosphodiesterases (Beavo et al. 1970; Butcher and Sutherland 1962; Cardinali 1980; Nicholson, Jackman, and Wilke 1989), but the relevance of the other mechanism proposed may be restricted by the comparatively large effective concentrations required.

4. Methylxanthines as pharmacological tools

All natural methylxanthines have been attributed specific pharmacological uses. The fact that such relevant biological effects are combined with relatively low toxicity, makes methylxanthines very tempting and intriguing therapeutic prospects. Caffeine potently stimulates the Central Nervous System (CNS) and respiratory system, while is very effective in cardiac stimulation, coronary dilatation and smooth muscle relaxation. Regarding theobromine, its most notable action would be as a cardiac stimulant (Riksen, Smits, and Rongen 2011). It is possible to rank the relative potency of each of the natural methylxanthines in every of these contexts (Table 2).

Other than the therapeutic uses already established for methylxanthines in medicine (a chronology is depicted in Fig. 1), new contexts where they are hinted to hold positive outcomes are being proposed. That has raised interest not only in methylxanthines but also in methylxanthine-containing dietary products, some of them very common. Regarding the two main methylxanthine sources for which beneficial effects have been recognized for more time, the rewarding effects of coffee and tea consumption are well characterized. Coffee (and caffeine) ingestion is known to propitiate an increase in energetic arousal, an improvement in hedonic tone, an increase in self-reported alertness, an improvement of psychomotor performance and in concentration (Nehlig 2010a; Nehlig 2015; Ruxton 2008). However, at higher doses (>200 mg), caffeine may cause anxiety and other unpleasant effects (Brice and Smith 2002; Childs and Wit 2006). As for tea, it has been proposed as a promising agent for the prevention and treatment of several human diseases, and some of the reported effects have been related, at least in some degree, with methylxanthines profile and total content (Carvalho et al. 2010; Jiao et al. 2015; Nunes et al. 2014; Schuller et al. 2004). At least some of the beneficial effects attributed to methylxanthines could be associated, at least in part, with their high antioxidant capacity (Azam et al. 2003; Grucka-Mamczar et al. 2009; León-Carmona and Galano 2011). In the following subsections we discuss the methylxanthine pharmacological use or potential within the context of selected health problems.

4.1. Respiratory disease

Methylxanthines have efficiently been therapeutically used in a number of disease contexts. Respiratory disease should be, however, the context in which methylxanthine medicinal use is more familiar. Curiously, each of the three main natural methylxanthines, caffeine, theophylline and theobromine, has been preferentially used in the treatment of specific different conditions (apnea of prematurity, asthma and cough respectively).

The first therapeutic applications of methylxanthines were discovered in the context of asthma treatment. The bronchodilatory effects attributed to methylxanthines in this context are thought to be elicited by relaxation of human airway smooth muscle, through inhibition of phosphodiesterases (Barnes 2005; Barnes 2013). Increase in cAMP levels would also inhibit the activation of inflammatory cells (Barnes and Pauwels 1994). Adenosine receptor blockade has also been proposed as a putative therapeutic mechanism in asthma treatment (Fozard and McCarthy 2002; Russo, Arcidiacono, and Polosa 2006).

Table 2. Ranking methylxanthine effectiveness in different pharmacological contexts (from (Beale Jr. 2011; Gardenhire 2016; Tarka and Cornish 1982)).

CNS Stimulation	*Caffeine>Theophylline>Theobromine*
Respiratory Stimulation	*Caffeine>Theophylline>Theobromine*
Coronary Dilatation	*Theophylline>Theobromine>Caffeine*
Cardiac Stimulation	*Theophylline>Theobromine>Caffeine*
Smooth Muscle Relaxation (Bronchodilation)	*Theophylline>Caffeine; Theobromine*
Diuresis	*Theophylline>Caffeine >Theobromine*
Skeletal Muscle Stimulation	*Caffeine>Theophylline>Theobromine*

Methylxanthines may also produce beneficial effects in bronchial asthma by chitinase inhibition (Tsirilakis et al. 2012). These enzymes have been proposed to play a pivotal role in the pathogenesis of the disease (Lee et al. 2014) and were found to be overexpressed in the asthmatic lung (Rao et al. 2005).

Theophylline is considered a rather potent bronchodilator (Stavric 1988a), and has been widely used in asthma context for a long time now since it was introduced as a clinical treatment for the condition in 1922 (Barnes 2013). Theophylline appears to diffuse better in bronchial tissue than other methylxanthines (van Zyl et al. 2008), and this should justify its preferential use over the others. However, relatively high plasma concentrations of theophylline (10–20 mg/L) are needed to achieve bronchodilation effects comparable with those of β_2-agonists, and at doses that inhibit phosphodiesterases, however several side effects may arise from the pharmacological use of this methylxanthine (Barnes and Pauwels 1994; El-Bitar and Boustany 2009). Currently, theophylline is recommended as an additional bronchodilator if asthma remains difficult to control after high doses of inhaled corticosteroids, plus long-acting β_2-agonists (Wilson, Gibson, and Coughlan 2000). Doxofylline is another *xanthine* derivative that has also been proposed to be an effective bronchodilator (Dini and Cogo 2001). Doxofylline differs from theophylline by the presence of a dioxolane group in position 7 (Goldstein and Chervinsky 2002). Doxofylline has been reported to hold similar efficacy, along with better tolerability profile than theophylline (Sankar, Lodha, and Kabra 2008). This improved safety profile may have to do with the absence of affinity towards adenosine receptors (Cirillo, Barone, and Franzone 1987).

As for asthma, theophylline was also used as a bronchodilator (in the same concentration range as in asthma) in the treatment of chronic obstructive pulmonary disease (COPD) for decades, but has lost popularity in this context as better tolerated and more effective bronchodilators have been introduced (Barnes 2006). Chronic obstructive pulmonary disease is a common chronic inflammatory disease of the lungs and methylxanthine positive effects on this condition have been associated with an anti-inflammatory action (Barnes 2013). This action should be related with an effect on histone deacetylase activity, resulting in suppression of inflammatory genes and enhancement of the anti-inflammatory effects of glucocorticoids (Cosio et al. 2004; Ito et al. 2002). This mechanism may also account for some of the anti-asthmatic effect of theophylline (Ito et al. 2002).

Other than their therapeutic use against asthma, compounds from the xanthine family have been clinically used for a long time as first-line, safe and effective, ventilatory stimulants for the treatment of apnea of prematurity (Abu Jawdeh et al. 2013; Chardon et al. 2004). In fact, methylxanthines have been used in clinical practice since the 1970's as the major pharmacotherapy for this condition (Aranda et al. 1977; Comer, Perry, and Figgitt 2001; Uauy et al. 1975). Recurrent apnea is uneasily common in preterm infants, particularly at very early gestational ages. It has been suspected to affect over 85% of neonates born at less than 34 weeks gestation, and in virtually all neonates born with less than 28 gestation weeks (Eichenwald, Aina, and Stark 1997; Fenner et al. 1973; Hofstetter et al. 2008). Apnea is a cessation of breathing due to immaturity of the respiratory drive, followed by decreased oxygen saturation in the blood and bradycardia. It may be severe enough to require the use of positive pressure ventilation (Henderson-Smart and De Paoli 2010). Methylxanthines have proved to be effective in reducing the number of apneic attacks in the short term, as well as in reducing the need for mechanical ventilation.

Caffeine and theophylline (also aminophylline) have been the gold standard treatment for countering this condition and reduce its consequences, but concerns about serious side effects, such as convulsive seizures, still subsist (Bhatia 2000; El-Bitar and Boustany 2009; Korematsu et al. 2008). Caffeine administration (administered at 20 mg/kg doses, orally or intravenously (Mueni, Opiyo, and English 2009)) is encouraged (with regard to theophylline, doses of 2–6 mg/kg/day (Mueni, Opiyo, and English 2009)) since, while displaying similar short term benefits (Bhatia 2000; Henderson-Smart and De Paoli 2010), short term side effects, such as tachycardia or feed intolerance, appear to be mitigated by treatment with this compound (Aranda et al. 2010; Bhatia 2000; Comer, Perry and Figgitt 2001; Henderson-Smart and De Paoli 2010). Caffeine was proposed to present a wider therapeutic window as well (Åden 2011; Schoen et al. 2014). Apparently, also financial advantages go along with the improved clinical outcomes, to side with caffeine over theophylline for apnea of prematurity treatment (Aranda et al. 2010; Schoen et al. 2014). Caffeine, improves minute ventilation, CO_2 sensitivity, diaphragmatic contraction, respiratory muscle function, and neural respiratory drive, while decreasing the hypoxic depression of breathing (Aranda et al. 2010). Caffeine presumably affects both the central and peripheral chemoreceptors that control ventilation. Also, it has been reported to significantly increase the resting hypoxic and hypercapnic ventilatory responses in humans (D'Urzo et al. 1990; Pianosi et al. 1994), which are controlled primarily by the peripheral chemoreceptors located in the carotid bodies. Several studies conducted in different animal species substantiate methylxanthine improvement of respiratory output (Eldridge, Millhorn, and Kiley 1985; Hedner et al. 1985; Herlenius and Lagercrantz 1999; Kawai et al. 1995; Lagercrantz et al. 1984; Wennergren and Wennergren 1983). Despite methylxanthine success in stimulating neonatal breathing and the reported mechanistic clues available, their mechanism of action as respiratory enhancers is subject of different interpretations. While most studies assign this therapeutic effect to an antagonism of adenosine receptors in central respiratory centers (Eldridge, Millhorn, and Kiley 1985; Hedner et al. 1985; Herlenius and Lagercrantz 1999; Kawai et al. 1995; Lagercrantz et al. 1984; Wennergren and Wennergren 1983), others ascribed it to inhibition of cAMP-dependent phosphodiesterase-4 in the neonatal carotid body (Mosca et al. 2014).

Finally, antitussive applications have also been anticipated for methylxanthines, namely theobromine. Theobromine, was reported to effectively inhibit citric acid-induced cough in conscious guinea pigs *in vivo* (Usmani et al. 2004). In fact, the same study reported a beneficial effect in humans as well. In this randomized double-blind study in healthy human volunteers, theobromine (a single oral dose of 1000 mg) proved to increase the capsaicin (a tussive stimulant) concentration required to induce five coughs on subjects (Usmani et al. 2004). Theobromine seems to suppress cough by inhibiting the

activation of afferent nerves, an effect supposedly elicited by suppression of phosphodiesterase activity and inhibition of bronchoconstricting adenosine A_1 receptors, though other modes of action may be involved (like the activation of Ca^{2+}-activated K^+ channels) (Smit 2011; Usmani et al. 2004). Theobromine antitussive action does not induce the side effects displayed by other antitussive drugs. Therefore, theobromine was even proposed as the basis for the design of a new class of antitussive drugs (Usmani et al. 2004).

4.2. Cardiovascular disease

There have always been more or less generalized concerns regarding the effects of caffeine consumption on cardiovascular activity, and it is commonly agreed that high coffee intake may cause tachycardia, palpitations plus a rapid rise in blood pressure, and a small decrease in heart rate (Fredholm et al. 1999). However, the fact is that it is currently accepted that moderate caffeine intake (up to three cups of coffee) does not adversely affect cardiovascular health (Nawrot et al. 2003; Riksen, Smits, and Rongen 2011). Although not necessarily in a detrimental manner, systemic administration of methylxanthines can profoundly affect hemodynamic parameters, such as blood pressure and heart rate (Riksen, Smits, and Rongen 2011). These changes in cardiac hemodynamics are expected to result from direct effects on myocardial contractility and conduction, on vascular tone, and on the sympathoadrenal system (Riksen, Smits, and Rongen 2011). Methylxanthines (caffeine, theobromine, and theophylline) have been reported to display an active vasodilator action on the coronary vessels, with increasing effects ranging from caffeine to theobromine (Tarka and Cornish 1982).

Caffeine administration (250 mg intravenous (Cameron, Modell, and Hariharan 1990) or 100 mg orally (Okuno et al. 2002)) was reported to improve the microcirculation of blood vessels in humans, while acutely increasing blood pressure (2.2 mg/kg) (Lovallo et al. 2004; Whitsett, Manion, and Christensen 1984). Positive chronotropic and inotropic effects were also reported for methylxanthines in humans and animal models (Cappelletti et al. 2015; Satoh 1993; Scholz 1984). The mechanism responsible for such effects was proposed to involve increased cAMP levels due to inhibition of phosphodiesterase (Riksen, Smits, and Rongen 2011). Adenosine receptor antagonism should not be involved in these particular actions of methylxanthines, since the inotropic effects of theophylline and adenosine are in fact opposite in atria, but similar in atrial and ventricular preparations (Scholz 1984).

Methylxanthines have been pharmacologically used in the management of cardiovascular conditions. An example would be the use of theobromine in the context of congestive heart failure and in the management of anginal syndrome (Batterman et al. 1959). Methylxanthines have also been successfully employed in the treatment of bradyarrhythmias, in particular when involving increased extracellular adenosine appearance (Cawley, Al-Jazairi, and Stone 2001; DeLago, El-Hajjar, and Kirnus 2008). These studies illustrate the potential of the pharmacological use of methylxanthine derivatives, with higher biological activity, in the treatment of cardiovascular diseases, which remain the leading death cause in modern societies.

Epidemiologic studies do report a degree of cardioprotection promoted by methylxanthine consumption. Long-term moderate consumption of coffee and tea (typically 1–3 cups per day) were linked to reduced risk of both coronary heart disease and stroke in healthy individuals (Bohn et al. 2012). However, the reported beneficial effects may not be (at least completely) ascribed to methylxanthines, since other compounds present (namely polyphenols) also have been proposed to elicit positive outcomes (Bohn et al. 2012). Some studies specifically considered coffee consumption only, reporting that moderate coffee consumption (1–3 cups/day in the United States or 3–4 cups/day in Europe) may reduce the risk of stroke and limit its consequences (Ding et al. 2014b; Larsson and Orsini 2011). The reduction in stroke incidence was found for both ischemic and hemorrhagic stroke and for both sexes (Larsson and Orsini 2011). The lowest cardiovascular disease risk is proposed to be obtained with a coffee consumption of 3 to 5 cups per day (Ding et al. 2014b).

Another interesting recently reported action of methylxanthines with impact on cardiovascular health is the effect of theobromine in increasing high-density lipoprotein (HDL) cholesterol. Low serum HDL cholesterol is considered an independent and inverse cardiovascular disease risk factor (Assmann and Gotto 2004). Cacao and cacao-derived products consumption was shown to increase plasma HDL cholesterol and decrease plasma low-density lipoprotein (LDL) cholesterol concentrations, contributing for cardiovascular protection and reduced risk of coronary heart disease, as observed in several clinical trials (Baba et al. 2007; Khan et al. 2012; Kris-Etherton et al. 1994; Mellor et al. 2010; Mursu et al. 2004). This beneficial effect of cocoa should indeed be assigned to theobromine and not to other possible phytochemicals, like flavonoids as previously hypothesized, since it was shown to independently and significantly increase HDL-cholesterol concentrations without a significant main effect of cocoa itself or an interaction effect (Neufingerl et al. 2013). Theobromine-induced (daily 850 mg) elevation in HDL cholesterol levels is pointed as not being necessarily adenosine receptor-dependent (Martínez-Pinilla, Oñatibia-Astibia, and Franco 2015), and increased levels of apolipoprotein-A-I were suggested to contribute to that effect (Neufingerl et al. 2013). Although some of the mechanisms involved are known, more studies are still necessary concerning the effects of methylxanthines to the cardiovascular system. That will open new perspectives on how these dietary-available compounds may occasion useful strategies to counteract cardiovascular disorders.

4.3. Cancer

Several evidences have been gathered typifying positive outcomes of methylxanthine consumption/administration in cancer contexts. Several methylxanthine-containing products have been hinted to induce beneficial outcomes, as is the case of cocoa extracts (in the treatment of human breast cancer (Oleaga et al. 2011), and coffee which is suggested to have a protective action towards colon cancer in several epidemiological publications (Printz 2015)). Several studies also showed that tea extracts display antimetastatic effects (Carvalho et al. 2010; Roomi et al. 2006), and anticancer potential against renal cell

carcinoma (Carvalho et al. 2010) and bladder cancer (Roomi et al. 2006), although in this case chemopreventive and chemotherapeutic effects are still a matter of some controversy (Conde et al. 2015). Caffeine seems to be important for the carcinogenic protective characteristics of tea, since decaffeinated teas present very low (or even none) cancer inhibitory properties (Huang et al. 1997).

Through time, conflicting reports were published suggesting mutagenic potential for caffeine (Dambrosio 1994; Lachance 1982; Rosenkranz and Ennever 1987), although today it is assumed that the regular and normal consumption (< 300 mg caffeine per day) would not result in mutagenic effects in humans (Dambrosio 1994; Nawrot et al. 2003). In fact, caffeine has been related with cancer-protective outcomes, since it was shown to inhibit tumor proliferation (0.044% caffeine in water for 22 weeks (Lu et al. 2006b) or 0.3% for 3 days, both in mice (Ryzhov et al. 2007)) and vascularization (exposition of cancer cell lines to caffeine 10 μM for 1 h) (Merighi et al. 2007). Several types of cancer may be even positively impacted by caffeine, according to studies conducted in animals. That would be the case of skin (Huang et al. 1997; Lu et al. 2002; Lu et al. 2006a), lung (Chung et al. 1998; Lu et al. 2006b) and mammary (Yang et al. 2005) cancers. In mice (a 100 mg/kg dose) (Gude, Menon, and Rao 2001) and posteriorly in melanoma cell lines, (up to 5.0 mM and 3 h treatment) (Shukla and Gude 2003), caffeine was shown display anti-metastatic activity. Therefore, it was suggested that it inhibits the invasion and proliferation in melanoma pulmonary metastasis as well as in high-grade tissue sarcoma (Shukla and Gude 2003). It has also been suggested that, mechanistically, caffeine beneficial effects are p53 independent (Lu et al. 2002) and may involve the promotion of cell cycle arrest in the G0/G1 phase in cancer cells, probably through suppression of cyclin D1-cdk4 complex activation and consequent inhibition of retinoblastoma protein phosphorylation (Hashimoto et al. 2004).

Other than caffeine, theobromine has also been related with positive effects in cancer. In fact, theobromine was reported to inhibit angiogenesis in tumor growth (Barcz et al. 2000; Barcz et al. 1998; Gil et al. 1993). In this case, theobromine action is thought to be mediated by its interaction with adenosine A_2 receptors (Barcz et al. 2000; Gil et al. 1993). Also, theobromine has shown antitumor potential in malignant glioblastoma proliferation, an effect supposed to be elicited by negative regulation of phosphodiesterase 4, promoting cAMP elevation and increasing the activity of p38 mitogen-activated protein kinase and c-Jun N-terminal kinase, while attenuating p44/42 extracellular signal-regulated kinase activity and the Akt/mammalian target of rapamycin kinase and nuclear factor-kappa B signal pathways (Sugimoto et al. 2014). The positive outcomes elicited by theobromine in this context lead the authors to suggest a rationale for a nutritional approach that could include products containing cocoa bean extracts, with significant theobromine content, for the prevention of human brain tumors (Sugimoto et al. 2014). Finally, theophylline (20–25 mg/ml, a range of concentrations close to that thought to be achieved when used as anti-asthma treatment) was reported to be able to induce cell death in carcinoma cell lines derived from human ovarian, prostate and lung cancer (Hirsh et al. 2004). Some studies also revealed advantages in the use of theophylline in the context of chronic lymphocytic leukemia (Basu and Mitra Basu 2000; Makower et al. 1999), an effect reportedly involving promotion of apoptosis.

Other than a direct mechanistic effect on cancer, methylxanthines were also shown to display the ability of enhancing the tumoricidal effect of standard antitumor drugs, such as cisplatin, thiotepa, doxorubicin, cyclophosphamide, mitomycin C, vincristine and methotrexate (Fingert, Chang, and Pardee 1986; Fingert et al. 1988; Hayashi et al. 2005; Kakuyama and Sadzuka 2001; Kawahara et al. 2008; Miwa et al. 2010; Takahashi et al. 1998; Tsuchiya et al. 1992). In fact, caffeine-assisted chemotherapy was suggested as a viable treatment option for different cancer manifestations (Hayashi et al. 2005; Miwa et al. 2010; Tsuchiya et al. 1992). However, caffeine was not the only methylxanthine shown to hold positive synergistic effects with drugs used in cancer chemo-treatment; theobromine and pentoxifylline also showed promising results (Fingert, Chang, and Pardee 1986; Kakuyama and Sadzuka 2001).

The synergistic effect of methylxanthines (namely caffeine) with antitumor drugs that induce DNA damage during cancer management, is supposed to result from a modulating effect as a DNA repair inhibitor (Iliakis et al. 1986). This effect would impact postreplication repair of sublethally damaged DNA, resulting in increased number of lethal chromosomal aberrations (Byfield et al. 1981; Fingert, Chang, and Pardee 1986), therefore enhancing cytotoxicity and antitumor activity. In fact, caffeine was reported to directly inhibit enzymes involved in DNA repair, as shown for DNA-dependent protein kinase DNA-PK, which is essential for the repair of DNA double-strand breaks (Block et al. 2004). However, it seems that most of the effects on DNA repair impairment exerted by caffeine and its derivatives are associated with possible arrest or abrogation of the cell cycle checkpoints, namely the G2/M checkpoint (Bode and Dong 2007; Kawabe 2004; Sabisz and Skladanowski 2008; Zhou et al. 2000). This checkpoint is important for DNA repair and prevents the replication of damaged DNA and the propagation of genetic abnormalities. In fact, a large group of xanthines were assayed for G2/M checkpoint inhibition assessment, with caffeine being reported as the most effective (Jiang et al. 2000). Another possible mechanism involved in caffeine chemotherapy enhancement would be the induction of rapid apoptosis in spindle checkpoint-arrested cells, in a pathway involving p21-activated kinase 1 (Gabrielli et al. 2007). In the case of methylxanthine synergy with doxorubicin in the promotion of anti-cancer action, it may not be related to inhibitory effects on DNA repair, but rather to specific increases in doxorubicin concentration by an inhibition of doxorubicin efflux from the tumor cells (Sadzuka, Mochizuki, and Takino 1995).

As for chemotherapy, methylxanthines also seem to promote a sensitizing effect towards radiotherapy, as reported in several cell lines (Busse et al. 1978; Malki, Gentry, and Evans 2006; Youn et al. 2009). The sensitization mechanism would also involve cell cycle interference, again probably involving G2/M checkpoint arrest, leading to jeopardized damaged-DNA repair (Asaad et al. 2000; Jha et al. 2002; Sarkaria et al. 1999; Wang et al. 2003; Youn et al. 2009). Methylxanthines were also suggested to be useful if used along with tumor therapies that are detrimentally affected by the presence of hypoxia, as is

thought to be the case of radiotherapy (Bush et al. 1978; Dische et al. 1983), since they were reported to generate substantial improvements in tumor oxygenation and perfusion (Kelleher, Thews, and Vaupel 1998). Finally, other beneficial effects elicited by caffeine in the context of cancer treatments may occur by modulation of their toxic side effects. In fact, chronic pretreatment with caffeine was reported to produce a significant degree of radioprotection (Farooqi and Kesavan 1992), and topical or intratumoral application was shown to decrease toxic side-effects in animal models, without changes in efficacy (Hebbar et al. 2002). These studies reinforce the evidences that methylxanthines do in fact display a meaningful pharmacological potential to be used either directly used or as co-adjuvants in cancer treatments. Nevertheless, epidemiological studies are still needed to clarify the safety of these therapies and *in vitro*/*in vivo* models are necessary to unveil the specific mechanisms underlying the anticancer activity of methylxanthines.

4.4. Obesity and diabetes

Claims have been made for positive outcomes of dietary methylxanthines and methylxanthine-containing products within the scope of obesity. For instance, regarding tea, many mechanisms have been proposed to substantiate its effect counteracting obesity by impacting metabolism through different mechanisms, including lipase inhibition (Chantre and Lairon 2002), stimulation of thermogenesis (Chantre and Lairon 2002; Dulloo et al. 1999; Dulloo et al. 2000), appetite modulation (Liao 2001), and synergism with caffeine (Kovacs et al. 2004; Zheng et al. 2004). But the question raised here is how much of these effects associated with methylxanthine-containing products may in fact be attributed to methylxanthines themselves. Several studies were conducted in humans addressing methylxanthine effect on the management of obesity and suggested that caffeine intake is inversely associated with body weight increase (Lopez-Garcia et al. 2006; Westerterp-Plantenga, Lejeune, and Kovacs 2005). Moreover, caffeine was reported to interfere with glucose and fatty acid metabolism, reinforcing its possible repercussions in body weight (Sugiura et al. 2012).

A lipotropic effect was proposed in the 1940's for caffeine, theophylline, and theobromine (Heppel, Porterfield, and Peake 1947) and another study incorporating these three methylxanthines showed that they generally inhibited the elevation of body fat percentage in developmental-stage rats, suggesting a possible role in the prevention of childhood obesity (Inoue et al. 2006). In this study, caffeine was also shown to reduce visceral fat in the abdominal cavity, which was in line with the results of a previous study implying an association between long-term dietary exposure to low-dose caffeine (0.05% caffeine in diet for 16 weeks) and decreased body fat (Zheng et al. 2004). The effect of caffeine on body weight may be linked to an induced decrease in the serum triglyceride level, which may restrict the supply of fatty acid to adipose tissue and result in body fat reduction (Inoue et al. 2006). However, the mechanism that has been more consistently involved in caffeine-elicited body fat decrease, involves the modulation of lipolysis (lipid breakdown into glycerol and fatty acids). Caffeine, as well as other methylxanthines, has been described to stimulate lipolysis *in vitro* (Acheson et al. 2004; Bray, Mothon, and Cohen 1970; Kim et al. 2010; Kuo and De Renzo 1969). Caffeine was proposed to prompt a decreased dependence from glycogen use (Spriet et al. 1992), switching the substrate preference from glycogen to lipids by stimulating hormone-sensitive lipase activity (an enzyme determinant for lipolysis (Okazaki et al. 2002)) and inhibiting glycogen phosphorylase activity (Rush and Spriet 2001). Hormone-sensitive lipase activation should derive from inhibition of phosphodiesterase activity and the resulting increase cAMP levels in adipocytes (Morimoto et al. 2001).

A diuretic effect has also been linked to methylxanthines for a long time (Davis and Shock 1949). In fact, until more potent diuretics were discovered by the middle of the last century, caffeine and theophylline (at doses > 250 mg) were traditionally used to increase urine output (Osswald and Schnermann 2011). The diuretic potency of methylxanthines was established in a number of animal and human studies to be theophylline > caffeine > paraxanthine > theobromine (Osswald and Schnermann 2011). Caffeine doses eliciting significant acute diuresis have been reported to be in the 300 mg range (about 4–5 cups of coffee) (Grandjean et al. 2000; Maughan and Griffin 2003; Passmore, Kondowe, and Johnston 1987; Riesenhuber et al. 2006). However, the extent of previous caffeine exposure may decrease its diuretic effectiveness (Izzo et al. 1983) illustrating the fact that this effect is highly dependent of dietary habits and synergistic action of caffeine with other compounds.

Methylxanthines also promote natriuresis. In fact, methylxanthine-elicited raise in urine flow may be concomitant with increased excretion of sodium, chloride, calcium, phosphate, magnesium and other urinary solutes (Osswald and Schnermann 2011).

The mechanisms taking place at the kidney level underlying the diuretic and natriuretic effects of methylxanthines remain unclear, but adenosine receptor antagonism and phosphodiesterase inhibition may be involved. Pharmacological blockade of A_1 adenosine receptors was in fact reported to promote diuresis and natriuresis, resulting in inhibition of proximal tubular reabsorption (Knight, Bowmer, and Yates 1993; van Buren et al. 1993; Wilcox et al. 1999), and A_1 receptors have been reported to be necessary for caffeine and theophylline-induced inhibition of renal reabsorption (Rieg et al. 2005). On the other hand, phosphodiesterase inhibition in the proximal tubule has also been suggested to contribute to the diuretic and natriuretic effects of methylxanthines (Coulson and Scheinman 1989; Fredholm, Hedqvist, and Vernet 1978).

Another field of research that has been disclosed for methylxanthines, concerns their putative usefulness within the sphere of diabetes. Diabetes mellitus is one of the greatest health threats arising from the modern global dietary options and daily habits. It is classified as type 1 or 2, with type 1 involving complete lack of insulin-production, while type 2 is characterized by impaired insulin secretion and increased insulin resistance (Association 2010). Epidemiological and prospective studies have in fact insinuated a connection between coffee consumption and a decreased risk of developing type 2 diabetes mellitus (Bhupathiraju et al. 2013; Bidel et al. 2006; Biessels 2010; Muley, Muley, and Shah 2012; Paynter et al. 2006; Sartorelli et al. 2010; van Dam and Feskens 2002; van Dam and Hu 2005). A recent meta-analysis proposed that the relationship between coffee consumption and the risk of developing type 2

diabetes mellitus occurs in an inverse dose–responsive manner, with protection increasing progressively from no or rare coffee consumption to 6 cups/day, in 1-cup-a-day increments (Ding et al. 2014a). However, caffeine direct involvement in the promoted protection towards the disease induced by coffee is a matter of controversy. It seems that caffeine may not be the only responsible for the effects produced by coffee, since both caffeinated and decaffeinated coffee were associated with reduced diabetes risk (Ding et al. 2014a; Pereira, Parker, and Folsom 2006; van Dam et al. 2006). Moreover, caffeine was reported to decrease glucose uptake (with a 5 mg/kg single oral dose) (Greer et al. 2001) and also increase insulin insensitivity (with a 3 mg/kg single intravenous dose, and posterior continuous infusion to maintain blood concentration) (Keijzers et al. 2002) in humans. Therefore, attention should be payed to other phytochemicals present in coffee, like phenolic compounds, as prospective improvement agents within the context of diabetes other than caffeine.

Coffee is not the only methylxanthine-containing beverage for which beneficial effects towards type 2 diabetes mellitus incidence have been reported. Tea consumption has also been associated with a lower risk of developing the disease (Dieren et al. 2009; Yang et al. 2014). Studies in animals have pointed positive effects for tea consumption on prediabetic rats, reporting improved metabolic status and prevention of most of the heart-related deleterious effects evaluated (Alves et al. 2015). Moreover, tea protective effects also took place in the cerebral cortex and oxidative profile of the prediabetic rat model, after two months of tea consumption (Nunes et al. 2015). Tea also proved to decrease glucose intolerance and increase insulin sensitivity in the same animal models (Alves et al. 2015) and was therefore suggested as an alternative co-adjuvant in the treatment or prevention of diabetes pathophysiology (Nunes et al. 2015).

Consistent proof of methylxanthine direct involvement in diabetes prevention is scarce and more targeted studies should be envisioned to address their putative effects. However, since both pancreatic cell insulin secretion (Seino et al. 2009) and liver glucose output (Vilela et al. 2014) are dependent on the intracellular concentration of cAMP, and since methylxanthines modulate phosphodiesterase activity (even though only at considerable concentrations, as we have discussed before), it has been speculated that these compounds may positively impact the glucose metabolism in humans (Sarriá et al. 2015). Theobromine may also be an interesting subject to investigate in this scope, since it was reported to reduce extracellular matrix accumulation and oxidative stress in the kidneys of diabetic rats (Papadimitriou et al. 2015). In fact, the authors of this study suggested Sirt-1 activation by theobromine to have therapeutic potential in the context of diabetic nephropathy.

4.5. Neurological and neurodegenerative disease

Taking into account that methylxanthines have the ability to cross the blood-brain barrier (Somani, Khanna, and Bada 1980) and that the adenosinergic system is omnipresent in the CNS (Trincavelli, Daniele, and Martini 2010), these compounds are expected to have a marked overall impact on neuronal function. In fact, the impact of methylxanthines in the nervous system is largely substantiated. Analgesic drugs exert their effects in various ways on the peripheral and central nervous systems. The use of methylxanthines, namely caffeine as an analgesic, especially as an analgesic adjuvant has been reported to maximize pain relief when combined with other common analgesics (paracetamol, ibuprofen or aspirin) (Derry, Derry, and Moore 2014; Laska et al. 1984). Methylxanthine (caffeine, pentoxifylline, and theophylline) anti-inflammatory action has been explained as the result from two main mechanisms: non-selective phosphodiesterase inhibition and as a non-selective adenosine receptor antagonism (Lee et al. 2014).

Another interesting effect of methylxanthines is the reported improvement of locomotive function. In the 1980's methylxanthines (caffeine and theophylline) were proposed to enhance locomotor activity in mice (Seale et al. 1986). Adenosine receptor antagonism was proposed as the main mechanism of action responsible for these locomotor activating effects of methylxanthines (Snyder et al. 1981). More recently paraxanthine was found to have a significantly stronger impact in locomotor activation than caffeine, theophylline and theobromine in rats. This study proposed, however, phosphodiesterase inhibition (most likely PDE9 inhibition) as the main mechanism responsible for such effects (Orrú et al. 2013). Other studies reinforce the beneficial effects of caffeine intake in improving motor activity in the context of neurodegenerative diseases, although trough mechanisms of neuroprotection and neurorestoration by trophic proteins (Airavaara et al. 2012; Chen and Chern 2011; Rosim et al. 2011).

Other beneficial effects traditionally reported for caffeine in the context of the nervous system include prophylactic effects on post-lumbar puncture headache (Nguyen and Walters 2014; Ragab and Facharzt 2014), and reduced neuronal damage after ischemic insult (in this case, with long-term administration of caffeine) (Rudolphi et al. 1989), as well as neuroprotective effects against spinal cord injury (SCI) (Rivera-Oliver and Díaz-Ríos 2014a). As for theophylline, it was reported to effectively suppress the occurrence of spike–wave discharges (followed by recording electroencephalograms) in a genetic model of absence epilepsy (WAG/Rij strain rats). The greatest suppression of spike–wave discharges in this model was achieved with 20 mg/kg theophylline (Ates, Sahin, and Ilbay 2004).

Probably the most commonly acknowledged effect of caffeine, and the reason why many people ingest it through coffee, is its psychostimulatory activity. Caffeine does produce a dose-dependent generalized psychostimulation trough CNS activation, resulting in sensations of increased alertness and ability to maintain an intellectual effort, along with decreased tiredness and fatigue, even in situations of sleep deprivation (Beaumont et al. 2005; Lozano et al. 2007). A similar psychostimulant effect was reported for chocolate, resulting from the combination of caffeine and theobromine in the proportions found in cacao (19 and 250 mg, respectively, representing a 50 g bar of dark chocolate) (Smit, Gaffan, and Rogers 2004). It was proposed that caffeine would exert its effects on alertness through CNS-mediated actions, while theobromine would be acting primarily via peripheral physiological changes (Mitchell et al. 2011).

Other than the aforementioned psychostimulant activity, cognitive benefits in humans have also been consistently

associated with caffeine alone (40–500 mg) (Lieberman 2001) or in combination with L-theanine, mimicking tea consumption (Giesbrecht et al. 2010). In animal models, evidence was gathered supporting a cognition-enhancing role for caffeine (0.3–10 mg/kg *ip*) in a variety of behavioral tasks that evaluated learning and memory (Angelucci et al. 2002; Takahashi, Pamplona, and Prediger 2008). Apparently, these effects do translate to humans (Haskell et al. 2005), and brief exposure to caffeine (a single-take of 250 mg in coffee) proved to improve memory and cognitive function in the scopolamine-induced amnesia model (Riedel et al. 1995). Moreover, caffeine was also reported to improve attention and information processing (Lorist and Tops 2003). In fact, caffeine has been suggested as a pertinent candidate for counteracting memory loss (Cunha 2008) and a significant number of prospective studies pointed protective effects against cognitive decline elicited by frequent coffee or caffeine consumption (Arab et al. 2011; Ritchie et al. 2010; Ritchie et al. 2007; Santos et al. 2010; van Gelder et al. 2006; Vercambre et al. 2013), although there are reports that do not validate such association (Laitala et al. 2009; van Boxtel et al. 2003). Other recent prospective data reported high plasma caffeine levels as being associated with reduced risk of dementia, particularly for those who already have mild cognitive impairment (MCI) (Cao et al. 2012). However, epidemiological studies in humans have yet failed to establish a causal relationship between caffeine/coffee consumption and a lower risk of dementia (Carman et al. 2014).

One of the main sources of the interest that currently surrounds methylxanthines, are their reported neuroprotective potential (Cunha 2005; Duarte et al. 2009; Guerreiro et al. 2008; Ritchie et al. 2007). A fair amount of scientific research has been conducted within this scope pointing plausible mechanisms of neuroprotection while some epidemiological studies suggest some promise. These neuroprotective effects have been better disclosed within the context of neurodegenerative disease. Sporadic Alzheimer's and Parkinson's diseases are the most common conditions accounting for the present worrisome neurodegenerative epidemic, but they still conceal unknown etiologies and are currently addressed with limited therapeutic resources. In fact, caffeine consumption has been related with a reduction in the incidence of two of the most prevalent neurodegenerative diseases, and evidences of such beneficial effects have been gathered from both animal and human studies (Alzheimer's (Arendash and Cao 2010; Eskelinen et al. 2009; Maia and de Mendonça 2002) and Parkinson's (Chen et al. 2001; Costa et al. 2010; Joghataie et al. 2004; Postuma et al. 2012)). In such complex neurological conditions as these, antagonism of the adenosine receptors, namely A_1 and/or A_{2A} receptor subtypes, was suggested to offer therapeutic benefits and to be the primary target of the neuroprotective effects of caffeine (Doré et al. 2011; Van der Walt and Terre'Blanche 2015). Another common mechanism for the beneficial effects of caffeine both in Alzheimer's and Parkinson's disease would be protection against blood-brain barrier dysfunction. This event has been implicated in the pathogenesis of Alzheimer's (Kalaria 1992; Kalaria 1999) and in Parkinson's as well, although more controversially (Kortekaas et al. 2005; Stolp and Dziegielewska 2009). However, chronic ingestion of caffeine was reported to hold a protective effect against blood-brain barrier dysfunction both in a rabbit model of sporadic Alzheimer's disease (3 mg in drinking water for 12 weeks) (Chen et al. 2008a) and also in a mouse model of Parkinson's disease (10 mg/kg, *ip*, for two weeks) (Chen et al. 2008b).

A considerable amount of studies conducted *in vitro* and in animal models and in animal models of neurodegenerative disorders have provided compelling physiologic support for caffeine's neuroprotective effects within the scope of these diseases.

In the case of Alzheimer's disease, the neuroprotective potential of caffeine has been demonstrated in mouse models. Both acute or long-term caffeine administration were shown to reduce brain amyloid-β- peptide (Aβ) production and accumulation in transgenic mice models of Alzheimer's disease and in cultured neurons taken from these animals (Arendash et al. 2009; Arendash et al. 2006; Cao et al. 2009; Chu et al. 2012), as well as in a rabbit model of the pathology (Prasanthi et al. 2010). Caffeine has also been reported to improve cognitive performance in animal models of Alzheimer's disease (Arendash et al. 2009; Arendash et al. 2006; Chu et al. 2012), and to restore memory and reverse the pathology in mice with pre-existing Aβ burden (Arendash et al. 2009).

The long-term neuroprotective effect of caffeine was proposed to take place by competitive antagonism of excessive activation of adenosine A_{2A} receptors in the hippocampus and cortex, which may attenuate the synaptoneurotoxicity induced by Aβ (Dall'Igna et al. 2007; Dall'lgna et al. 2003; Prediger, Batista, and Takahashi 2005). However, A_1 receptors may also play a role in caffeine-mediated neuroprotective effects. In fact, Alzheimer's disease patients showed a reduced density of adenosine A_1 receptors (Kalaria et al. 1990; Ułas et al. 1993) and the blockade of these receptors has been reported to promote cognitive benefits in rodents (Maemoto et al. 2004). Moreover, selective adenosine A_1 receptor antagonists were proposed as potential targets for the treatment of cognitive impairments, such as those occurring in patients with Alzheimer's and Parkinson's disease (Mioranzza et al. 2011; Pereira et al. 2002; Ribeiro and Sebastião 2010). Other complementary mechanisms that have been proposed to account for caffeine beneficial action in animal models of the disease are the ability of caffeine to decrease hippocampal levels of pro-inflammatory cytokines (a daily oral dose of $\approx$ 1.5 mg caffeine/mouse for 2 months) (Cao et al. 2009) increased caffeine-induced release of intracellular calcium in neurons (25 mM in cortical cultures) (Smith et al. 2005), enhanced brain mitochondrial function (0.3 mg in drinking water for two months, in mice) (Dragicevic et al. 2012) and increased cerebrospinal fluid production (0.6 g/L caffeine in water for 3 weeks, in rats) (Han et al. 2009; Wostyn et al. 2011).

The discussed findings are somehow supported by epidemiologic results. In fact, the main conclusion elicited from epidemiology is the establishment of a link between chronic caffeine/coffee consumption during the middle stages of life and a significantly lower risk of developing neurodegenerative diseases, namely Alzheimer's disease (Eskelinen et al. 2009). Both prospective (Eskelinen et al. 2009; Johnson-Kozlow et al. 2002; Lindsay et al. 2002; Ritchie et al. 2007; van Gelder et al. 2006) and retrospective (Maia and de Mendonça 2002) studies have investigated the impact of long-term consumption of caffeine

with regard to this pathology, linking chronic caffeine intake with lower risk for the incidence and mitigation of disease progression. In these studies, lifetime coffee intake is considered and regular consumption of coffee was defined as nearly everyday. Maximal protective action is described by several studies as being achieved by the consumption of 3 coffee cups per day. Despite all the evidence compiled from basic science and epidemiological studies, the etiology of Alzheimer disease remains unrevealed, and an unequivocal basis for caffeine-driven beneficial effects can only be speculated. Therefore, the promise of a putative caffeine-based therapy for Alzheimer's disease remains adjourned.

Similarly to Alzheimer's disease, caffeine has been linked to beneficial effects in the progression of Parkinson's disease, although the mechanisms involved in the process are also far from being clarified (Rivera-Oliver and Díaz-Ríos 2014b). Adenosine receptor blockade was first proposed in the 1970s as the mechanism for the protective activity of caffeine in the context of this disease (Fuxe and Ungerstedt 1974). However, the molecular mechanisms by which inhibition of adenosine receptors protects dopaminergic neurons from degenerating remains elusive. Both epidemiologic and experimental evidence converge, suggesting that caffeine and selective adenosine A_{2A} receptor antagonists represent interesting strategies to attenuate dopaminergic neurodegeneration in Parkinson's disease. In fact, studies performed in rat models revealed that caffeine administration prevented the loss of nigral dopaminergic neurons, indicating a role for caffeine in delaying neuronal degeneration (Chen et al. 2001; Li et al. 2008; Sonsalla et al. 2012). Moreover, chronic antagonism of adenosine A_{2A} receptors was shown to improve the motor deficits elicited by Parkinson's disease (Morelli, Carta, and Jenner 2009). The other well established molecular target for the treatment of Parkinson's disease is monoamine oxidase (MAO), particularly the MAO-B isoform (Petzer and Petzer 2015). Caffeine and, more efficiently, other caffeine-derived compounds have been shown to inhibit this enzyme (Petzer, Pienaar, and Petzer 2013), making the quest for effective dual-target-directed compounds, which would act at both major therapeutic targets hinted for Parkinson's disease, very appealing. Stabilization of the blood-brain barrier may be another mechanism by which caffeine counters Parkinson's disease (Chen et al. 2008b). Finally, anti-neuroinflammatory action combined with a reduction of neuron oxidative damage was also recently suggested as a plausible protection mechanism prompted by caffeine (Gołembiowska et al. 2013).

Several epidemiologic studies have also suggested an inverse, dose–response relationship between coffee/caffeine consumption and the risk of Parkinson's disease incidence (Ascherio et al. 2001; Benedetti et al. 2000; Costa et al. 2010; Palacios et al. 2012; Qi and Li 2014; Ross et al. 2000a; Saaksjarvi et al. 2007). Regarding the studies addressing coffee consumption, caffeine was suggested as being the causal factor of the prompted favorable effects (Palacios et al. 2012). This beneficial effect is also linked to consumption at midlife (in this case 2 or more cups of coffee per day). A very recent dose-response meta-analysis encourages the ingestion of 3 cups of coffee a day, since it may be the optimal protective dose of caffeine for Parkinson's disease prevention (Qi and Li 2014).

As for Alzheimer's disease, the proper mechanism of caffeine-induced protection is not fully clarified yet. Other than the beneficial clues listed before within the scope of Alzheimer's and Parkinson's disease, also Machado-Joseph disease appears to be favourably impacted by caffeine (Gonçalves et al. 2013). On the other hand, a retrospective study has recently linked caffeine to detrimental effects in Huntington's disease (Simonin et al. 2013), suggesting that the underlying mechanisms of its interference within the scope neurodegenerative diseases encompasses an intrinsic complexity that should indeed be further studied.

4.6. Human fertility

The impact of methylxanthines on human fertility as also been the focus of several studies. Interestingly, results greatly differ between sexes and remain under intense debate. A study showed that high maternal consumption of caffeine (more than 3150 mg/month, or about one cup of brewed coffee a day) could be related to reduced fertility in women trying to get pregnant (Wilcox, Weinberg, and Baird 1988). On the other hand, regarding male reproductive system, it is suggested that moderate consumption of caffeine should be safe (50 mM in cell lines, corresponding to a plasma concentration of 10 mg/mL (Dias et al. 2015)). Moreover, the nutritional support of spermatogenesis by Sertoli cells appeared to be enhanced after exposure to caffeine (50 μM), and this should result in a general improvement of male fertility (Dias et al. 2015).

Male infertility is unfortunately relatively common, accounting for about 50% of the problems affecting couples with fertility problems (Dohle et al. 2005). Usually, in situations of male subfertility or infertility, the condition is due to loss of sperm function rather than decreased number of spermatozoa (Hull et al. 1985) and thus sperm quality is a valuable marker for male reproductive health. Methylxanthines have been studied within the scope of sperm function, and unlike the aforementioned epidemiologic hints regarding female fertility, positive effects have been unveiled. A positive effect of methylxanthines (0.15–1.2 mM) on abalone sperm Ca^{2+} transport was reported, and the suggestion was made that their activity on sperm function could be mediated through changes in Ca^{2+} conductance (Kopf, Lewis, and Vacquier 1984). The activity of methylxanthines as phosphodiesterase inhibitors was also involved in the beneficial effects of methylxanthines, through regulation of cAMP levels. In fact, cAMP levels are positively correlated with increased motility (Tash and Means 1982) and there is evidence that cAMP-dependent phosphorylation is involved in the activation of spermatozoa motility when they are released from storage in the male reproductive tract (Brokaw 1987). Both mechanisms may in fact be decisive for fertilization, since increase in intracellular calcium and cAMP are reported to be important in several steps of the process (Yoshida, Kawano, and Yoshida 2008).

Among the common dietary products that contain methylxanthines, tea was the one recently proposed to elicit positive outcomes in male fertility. A tea extract (white tea), was reported to alter the glycolytic profile of cultured Sertoli cells, stimulating lactate production. Besides its importance as a metabolic substrate, a role as an anti-apoptotic agent in the developing germ cells was also proposed for lactate and, therefore, white tea consumption was suggested as being advantageous to male reproductive health (Martins et al. 2013). Notably, animal studies provided compelling

evidence that white tea consumption can counteract the deleterious effects of prediabetes on male reproductive health by improving sperm concentration and quality after two months of exposure to the drink (Oliveira et al. 2015). Interestingly, white tea was also suggested as a promising media additive for sperm storage at room temperature, helping to avoid the deleterious effects brought by refrigeration (Dias et al. 2014). These studies provide compelling evidence of the pharmacological potential of white tea, known to be rather methylxanthine-rich, in the context of male reproductive health.

Although many beneficial effects have been proposed for several tea components, namely catechins and L-theanine (Cooper 2012; Huber 2003; Matsui 2015), at least some of the beneficial effects proposed within the scope of male fertility may be specifically assigned to the caffeine content. Caffeine was shown to modulate Sertoli cell metabolism and promote, by itself, stimulation of lactate production at concentrations mimicking moderate dietary consumption (Dias et al. 2015). Moreover, caffeine (1.15 mM, in Beltsville thawing solution supplemented with $CaCl_2$) was also suggested as an effective additive in the context *in vitro* fertilization, since it was reported to improve the probability of pregnancy in gilts and sows by boar semen (Yamaguchi, Funahashi, and Murakami 2009). Nevertheless, more work will be needed within this scope in order to unveil the full potential of methylxanthines in the context of sperm conservation and, more broadly, in male fertility.

5. Detrimental effects

Taking into account that natural methylxanthines are thought to be biosynthesized by plants as a protection mechanism against insect feeding, and are biopesticidal at concentrations known to occur in plants (Nathanson 1984), concerns raised about putative toxicity are justified.

The toxicity of methylxanthines may greatly vary, depending on the specific compound and the animal in question (Table 3). In rats LD_{50}'s are 200 mg/kg for caffeine, 206 mg/kg for theophylline and 950 mg/kg for theobromine (Tarka and Cornish 1982). In humans, the values are relatively close to those in rats with LD_{50}'s of 192 mg/kg for caffeine, and 1000 mg/kg for theobromine. Thus, human acute toxicity towards methylxanthines is very low. For instance, for caffeine the acute toxic level should be about 10 g/day, which would be comparable to drinking 100 cups of instant coffee (Cappelletti et al. 2015). It is important to notice that, in fact, individuals vary in their sensitivity to methylxanthines, and some of those fluctuations may be genetically originated (Alsene et al. 2003; Hart, de Wit, and Palmer 2012; Rogers et al. 2010).

Nevertheless, methylxanthine acute toxicity in humans is rather low. Although a great inter-species variability may occur

Table 3. Methylxanthine toxicity parameters in man and rat (Tarka and Cornish 1982).

	LD_{50} (oral, mg/kg)		
	Caffeine	Theobromine	Theophylline
Man	*150–200*	*1000*	*(no data available)*
Rat	*200*	*950*	*206*

the values for humans (LD_{50}'s of 192 mg/kg for caffeine and 1000 mg/kg for theobromine) are very close to the ones reported for rats (Tarka and Cornish 1982) (Table 3). There is overwhelming scientific evidence proving that moderate consumption of caffeine from common sources is safe (2014; Glade 2010). Coffee/caffeine consumption should not be harmful up to doses of 200 mg in one sitting (about $2^1/_2$ cups) or 400 mg daily (about 5 cups) (Nehlig 2015). Therefore, daily caffeine ingestion was suggested to be harmless in terms of general toxicity, or in terms of detrimental consequences to cardiovascular function, bone status and calcium balance, cancer incidence and negative changes in adult behavior (Nawrot et al. 2003). However, deleterious effects may emerge from consumption of diet supplements enriched in caffeine (Pendleton et al. 2012; Pendleton et al. 2013) or if caffeine is combined with drugs of abuse (Sinchai et al. 2011). Thus, attention should be paid to the rapidly expanding energy drink market, since these beverages contain amounts ranging from 50 mg to alarming 500 mg per can or bottle (Cappelletti et al. 2015).

Acute toxicity due to excessive caffeine intake is not very common. When it occurs, it may elicit several intoxication manifestations, such as elevated respiration, gastrointestinal disturbances, insomnia, nervousness, headache, tachycardia, arrhythmia, nausea, seizures, and even death (Clauson et al. 2008; Nawrot et al. 2003). Reports describing death provoked by excessive intake of caffeine are scarce (Nawrot et al. 2003). The average post-mortem concentration of caffeine reported in fatal caffeine intoxication was 140 mg/L (Banerjee et al. 2014). Chronic effects raised by excessive caffeine consumption, may be expressed by dysfunctions involving the gastrointestinal and renal systems, liver and musculature (Nawrot et al. 2003; Stavric 1988b). Several sporadic studies have implied caffeine/coffee consumption in other detrimental actions. For instance, epidemiologic studies made an association between elevated coffee intake and increase risk of ischemic stroke (Mostofsky et al. 2010), what somehow contradicts some of the beneficial effects on vascular function discussed above.

An issue that has been raising controversy for some time is whether or not caffeine should be classified as a drug of abuse. Some say yes, since it creates dependence, highlighting its actions regarding positive reinforcement, tolerance promotion, and the existence of withdrawal syndrome after stopping its consumption (Lozano et al. 2007). Others disagree, saying that the relative risk of physical dependence to caffeine is quite low (Nehlig 1999) and that withdrawal is brief and relatively mild (Nawrot et al. 2003). Moreover, many studies claim that moderate coffee drinkers do not develop a physical dependence to caffeine at all (Nehlig 2015). A compelling vindication against the case of caffeine being a drug of abuse is brought by the realization that caffeine does not stimulate dopaminergic transmission in the shell of the nucleus accumbens (which is thought to be a specific feature of drugs of dependence (Nehlig 2004)) and that human imaging studies showed that it does not activate the brain circuit of dependence and reward (Nehlig, Armspach, and Namer 2010b).

Caffeine has also raised concerns in a sports context. Studies emerged pointing caffeine as a performance enhancer, namely in activities relying on explosive strength (Jacobson et al. 1992), short-term, high-intensity exercise (Anselme et al. 1992; Jackman et al. 1996), and activities depending on aerobic activity and endurance (Graham and Spriet 1991; Greer, Friars, and

Graham 2000; Kovacs, Stegen, and Brouns 1998). Caffeine use was regulated by the competent institutions, namely the International Olympic Committee, and a concentration of 12 mg/mL in urine was defined as the accepted upper limit (Chapman and Mickleborough 2009).

As for theophylline, it showed promise as CNS stimulant, although it is mainly used in respiratory disease therapy (namely chronic obstructive pulmonary disease and asthma (Barnes 2013)). It has also been proposed as having applications as a diuretic (Bell et al. 1998). Theobromine has showed significant less CNS activity than caffeine and theophylline, possibly because of physicochemical properties that hinder its distribution in the CNS (Salihović et al. 2014).

In both rodents and humans, theobromine seems to be safer than caffeine, since oral lethal doses are even higher (Franco, Oñatibia-Astibia, and Martínez-Pinilla 2013). Theobromine also seems devoid of carcinogenic effects (Rosenkranz and Ennever 1987). However, theobromine, is significantly toxic in other mammals, including pets (namely dogs) (Eteng et al. 1997; Smit 2011). The reasons that underlie this differential toxicity are not well established, but this should be a trademark example of a compound whose mechanisms of action significantly vary between humans and other mammals (Martínez-Pinilla, Oñatibia-Astibia, and Franco 2015). These toxic effects of theobromine in susceptible species may be enhanced since it displays a relatively higher half-life than caffeine (Baggott et al. 2013), increasing systemic exposure. The awareness of adverse effects in some animals, prompted clinical trials, generally subscribing the harmlessness of theobromine for humans in regular intake ranges (Baggott et al. 2013). Given its limited toxicity in humans, theobromine chronic effects and studies targeting them are very scarce. Nevertheless, one such study reported some side-effects (namely involved sweating, trembling and severe headaches) to be linked to long-term consumption of large quantities of cocoa products (the daily equivalent of l.5 g methylxanthines) (Czok 1974).

Although some similarity exists between theophylline and caffeine in terms of pharmacological and toxicological properties, the first has been suggested to display stronger toxic effects (Stavric 1988b). That was the reason for caffeine to be preferred over theophylline in the treatment of respiratory conditions (Henderson-Smart and De Paoli 2010; Schoen et al. 2014). The more pronounced toxic effects of theophylline may be related with its extended half-life, which is about twice that of caffeine (Gilbert 2004). Unwanted effects of theophylline are related to plasma concentration, and tend to manifest when plasma concentration exceeds 20 mg/L (Barnes 2013). Frequent side-effects of theophylline administration may include headache, nausea (vomiting even), increased acid secretion and gastro-esophageal reflux (Barnes 2013). At higher concentrations, theophylline may cause convulsions and cardiac arrhythmias (Barnes 2013; Stavric 1988a).

Chronic effects of theophylline should only occur insidiously in patients receiving the drug therapeutically (Sessler 1990; Tsai et al. 1994) and should almost always occurs as a result of chronic oral administration (Minton and Henry 1996). Chronic toxicity may result of doses that are too high or of particular factors which somehow jeopardize its clearance, as may be the case of concurrent medication changes or disease states (Minton and Henry 1996). The features of theophylline chronic exposure should be similar to those of acute toxicity. However, the differences noted should include increased susceptibility to the drug (Shannon 1993), and more frequent seizures and serious arrhythmias in patients who suffered chronic overdosing, induced at lower serum concentrations with regard to those given an acute single overdose (Olson et al. 1985). These reports led to clinical suggestions for patients with chronic theophylline poisoning to receive extracorporeal aid in drug removal (hemoperfusion or hemodialysis) (Heath and Knudsen 1987; Olson et al. 1985; Shannon and Lovejoy 1992).

Paraxanthine is the major metabolite of caffeine in humans, and its plasma levels are normally two thirds those of caffeine (Benowitz et al. 1995). Paraxanthine is thought to be a rather innocuous compound for humans (Stavric 1988c). Another caffeine metabolite, 1-methylxanthine, was shown to inhibit the transport activity of human organic anion transporter 1 *in vitro* (Rengelshausen et al. 2004), in a more potent manner than caffeine and other xanthine derivatives (Sugawara et al. 2005). This transporter is implied in the renal excretion of numerous drugs. This interference may alter the pharmacokinetics of clinically important drugs in humans (Babu et al. 2002; Takeda et al. 2002a; Takeda et al. 2002b). Therefore, caffeine, through its metabolite 1-methylxanthine, may modulate the toxic effects of other compounds, and this may also help explain the potentiating action of caffeine on the effects of other drugs.

Also, there is considerable evidence that should not be disregarded regarding possible detrimental actions of methylxanthines on male reproductive system, and that should be weighed against the positive effects discussed in the previous section. Methylxanthines (namely caffeine, theophylline and theobromine) were reported to promote testicular atrophy and aspermatogenesis (Friedman et al. 1979; Gans 1984; Weinberger et al. 1978). Theobromine was consistently reported to have detrimental effects on animal male reproductive system in a number of studies (Soffietti et al. 1989; Tarka, Zoumas, and Gans 1979). However, the concentrations of methylxanthine that lead to some of these effects are significantly high, and would be difficult to attain by human consumption (Tarka and Cornish 1982).

Despite the fact that the use of methylxanthine is commonly considered fairly safe on the doses achievable by normal consumption, the most common concern is still related with prenatal exposure. Methylxanthines may cross the placental barrier in humans, enabling fetus exposure (Skopiński et al. 2011), an event that may result in hazardous outcomes since the developing fetus may not possess the fully developed detoxification enzymes (Eteng et al. 1997). This is a field that has been somewhat overlooked and deserves special attention in the future.

Several studies have been conducted focusing on methylxanthine prenatal exposure and possible detrimental effects. Epidemiologic studies go either way in terms of reporting methylxanthine detrimental impact on pregnancy. An early

Table 4. Reported methylxanthine medical use.

	Condition	Methylxanthine	Doses	Proposed Mechanism
Respiratory	Asthma (Barnes 2013)	Theophylline	10–20 mg/L (55–110 mM)	phosphodiesterase inhibition (Barnes 2005; Barnes 2013)
				antagonism of adenosine receptors (Fozard and McCarthy 2002; Russo, Arcidiacono, and Polosa 2006)
	Chronic obstructive pulmonary disease (Barnes 2006)	Theophylline	10–20 mg/L	phosphodiesterase inhibition (Barnes 2006)
	Apnea of prematurity (Scanlon et al. 1992)	Caffeine	13–20 mg/L	antagonism of adenosine receptors (Eldridge et al. 1985; Hedner et al. 1985; Herlenius and Lagercrantz 1999; Kawai et al. 1995; Lagercrantz et al. 1984; Wennergren and Wennergren 1983)
		Theophylline	13–20 mg/L	phosphodiesterase inhibition (Mosca et al. 2014)
	Cough (Usmani et al. 2004)	Theobromine	32 mg/kg	phosphodiesterase inhibition and/or antagonism of adenosine receptors (Smit 2011; Usmani et al. 2004)
Cardiovascular	Congestive heart failure and anginal syndrome (Batterman et al. 1955)	Theobromine	single dose of 200 mg	(not suggested)
	Bradyarrhythmias (Benditt et al. 1983; Cawley et al. 2001)	Theophylline	9–12 mg/L	antagonism of adenosine receptors (Evoniuk, von Borstel, and Wurtman 1987)
	HDL cholesterol increase (Neufingerl et al. 2013)	Theobromine	daily 850 mg dose (28.75 ± 16.12 μM/L)	(not suggested)
Cancer	Chronic lymphocytic leucemia (Makower et al. 1999)	Theophylline	300 mg twice daily for at least a month	phosphodiesterase inhibition, modulation of protein expression (Makower et al. 1999)
	Cancer treatment enhancement (Hayashi et al. 2005;Miwa et al. 2010; Tsuchiya et al. 1992)	Caffeine	1.2–1.5 g/m^2/day for 3 days	G2/M checkpoint arrest (Kawabe 2004; Sabisz and Skladanowski 2008; Zhou et al. 2000).
Diuretics	Diuretics (Davis and Shock	Theophylline	480 mg	antagonism of adenosine receptors (Knight, Bowmer, and Yates 1993; Rieg et al. 2005; Wilcox et al. 1999)
	1949; Maughan and Griffin 2003)	Caffeine	>250–300 mg	phosphodiesterase inhibition (Coulson and Scheinman 1989; Fredholm, Hedqvist, and Vernet 1978)
Analgesic	Analgesic adjuvant (Derry et al. 2014)	Caffeine	>100 mg	maybe antagonism of adenosine receptors (Derry et al. 2014)
	Post-lumbar puncture headache (Ragab and Facharzt 2014)	Caffeine	500 mg	antagonism of adenosine receptors (Ragab and Facharzt 2014)

study showed that caffeine intake did not hold consequences on pregnancy outcome and general offspring development (Barr and Streissguth 1991). Other studies reported no effects for moderate coffee consumption on neonatal birth weight or the length of human gestation (Bech et al. 2007), on the incidence of cardiovascular malformation (Browne et al. 2007; Jahanfar and Jaafar 2013, 2015), or on the risk of birth defects (Browne et al. 2011). Others report that caffeine intake slightly increases the risk of fetal growth restriction (Group 2008), the risk of miscarriage (Weng, Odouli, and Li 2008), the risk of delivering a baby with spina bifida, anencephaly or encephalocele (Schmidt et al. 2009), increases "small for gestational age" (SGA) births (Hoyt et al. 2013), increases the incidence of congenital limb deficiencies (Chen et al. 2012), and increases the risk of delivering a male infant with neonatal cryptorchidism (in this case, only for intakes exceeding 400 mg/day) (Mongraw-Chaffin et al. 2008). Taking all these studies into account, and despite inconsistencies in the results, it may seem sensible to encourage pregnant women to limit coffee consumption, even more in the case of reproductive-aged women, who were proposed as a susceptible risk group (Kuczkowski 2009).

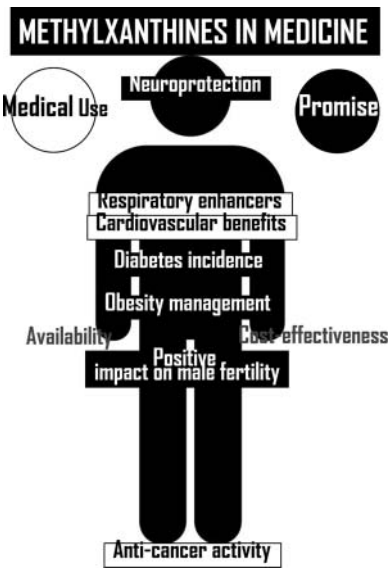


Figure 5. Impact and advantages of methylxanthines in human health.

Evidences of putative detrimental methylxanthine actions during pregnancy were also gathered from animal studies. Caffeine in moderate doses was shown to affect normal sexual differentiation of the fetal testes in rats (Pollard, Williamson, and Magre 1990). Another study reported that theobromine affected progeny development in both prenatal and postnatal periods. In that study, a theobromine-enriched diet significantly inhibited embryo growth and tissue proangiogenic activity in mice, and reduced neonatal relative limb size (Chorostowska-Wynimko et al. 2004). Skopinski and colleagues (Skopiński et al. 2011) finely reviewed the existing literature regarding prenatal exposure to methylxanthines in animals and concluded that prenatal exposure can produce changes in the developing organism that may persist in further stages of life. However, they also concede that inferences made upon the available data may

be premature and even controversial. In another recent review (Brent, Christian, and Diener 2011), the authors claim that animal studies reporting methylxanthine (in this case caffeine) detrimental effects on prenatal development employ concentrations that will not be achieved by human daily consumption. Thus, the authors concluded that normal human exposure should not impact spontaneous abortion or normal fetal growth.

6. Conclusions

The methylxanthine historical importance in medicine was discussed throughout this paper. Established (and other now obsolete) therapeutic uses (Table 4) remain under debate while other contexts where methylxanthines may have pharmacological interest were also unveiled. In fact, despite all the contexts positively impacted by methylxanthines listed before, others are emerging. However, given the scarce amount of studies available at this point, they did not justify an entire section yet. That is the case of hepatic (cholestatic liver injury and hepatitis C), kidney (of uric acid nephrolithiasis) and ocular (myopia) scopes.

Over the last decades, a great effort was made in order to understand the molecular mechanisms underlying methylxanthine detrimental or beneficial effects, and even those that motivate our craving for products rich in these compounds. However, what seems crucial to highlight from the research conducted so far, is the inherent potential that methylxanthines carry to meaningfully impact modern biomedical research.

Despite the previously listed detrimental effects attributed to the consumption of methylxanthines, if we weigh them against the beneficial effects also aforementioned (Fig. 5), we would probably reckon that health advantages outweigh potential harms, and we would tend to quickly encourage a moderate tea, coffee, or chocolate consumption. However, a more prolonged and thoughtful appreciation would compel us to be more careful, although we would probably still lobby for it. The problem is that, although "moderate consumption" should not be detrimental, what "moderate consumption" really means is not always available in a simple, accessible and quantified manner. And that should be a difficult task, taking into account all the idiosyncrasies involved that may impact the personal tolerance, and many other variables like interaction with other drugs, the specificity of disease contexts, and even environmental constraints. It seems evident that methylxanthines can be helpful in a variety of ways. Now, researchers will have to figure out how to potentiate those inherent virtues. If widespread methylxanthines use targeting pandemic diseases can be approved and regulated by official agencies, we will secure fairly inexpensive, readily-obtainable resources that may help us raise general well-being, and that may translate into efficacious prevention strategies to several disease-associated conditions.

Anyway, given all the promise attributed to these compounds, additional research on methylxanthines seems completely justified. New studies should be envisioned, maybe using dietary-relevant doses, since many experimental studies are conducted with physiologically irrelevant concentrations. Although these studies may help shedding some light to mechanistic questions, extrapolation will always be difficult and questionable. Although there may be constraints, well-designed epidemiologic trials encompassing a more precise clarification of dose–response relationships would permit better comparison with observational data and posterior translation into public health recommendations and dietary guidelines. It would also be useful if these studies could find ways to isolate the influence of methylxanthines in drinks/foods from that of other components. In the case of caffeine, for instance, making outcome associations with caffeinated or decaffeinated coffee consumption is a way of distinguishing the effects on which this methylxanthine had indeed an impact. Finally, with the increasingly easier access to state of the art procedures and equipment, like those involved in neuroimaging techniques, it should be expectable that substantial breakthroughs may be propitiated regarding the clarification of the mechanisms underlying the neuroprotective (or detrimental) effects of methylxanthine consumption.

While the doses attained physiologically by regular consumption appear to be safe, methylxanthine pharmacological concentrations may induce undesirable side-effects. Therefore, there is a margin to architect new, more efficient and less harmful molecular formulations based on methylxanthine structure. Structure-activity approaches may help generate novel selective cost-effective drugs displaying enhanced impact on specific human conditions, while encompassing more manageable toxic effects. This was already done to some extent in some specific contexts. Putative synergistic effects of methylxanthines in therapeutic cocktails may as well be a pertinent approach, and such approach should indeed justify some meaningful research. A more generalized and reasoned awareness of the beneficial actions of methylxanthine may pave the way for the emergence of new optimized cooperative therapy agents, but also of innovative functional foods. In fact, cocoa manufacturers are making experiments in production in order to provide new functional cocoa products which are enriched in specific bioactive components (polyphenols, methylxanthines or dietary fiber), with reduced energy content (fat and sugar). This may be a prolific area of research, with a great commercial interest. As discussed before, both methylxanthine-containing functional foods and novel derivatives would have a wide range of possible physiologic targets susceptible of being modulated, hopefully with relevant therapeutic outcomes. Moreover, other areas are emerging where methylxanthines may assume additional relevance. That is the case of cosmetology and dermatology (where caffeine is already used in anti-cellulite creams), taking advantage of caffeine high biological activity and ability to penetrate the skin barrier. That is also the case of possible anti-inflammatory therapeutic applications of novel methylxanthine derivatives (acting as mammalian chitinase inhibitors). Anyway, there is still a lot to figure out until we make the most of the promise raised by methylxanthine biochemistry. Luckily enough, we do have coffee, and tea, and even chocolate, to help us while paving the rest of the way.

Abbreviations

Aβ	amyloid-β- peptide
cAMP	cyclic adenosine monophosphate
CNS	central nervous system
COPD	chronic obstructive pulmonary disease

DNA	deoxyribonucleic acid
GABA	gamma-aminobutyric acid
HPLC	high-performance liquid chromatography
LD_{50}	median lethal dose
MAO	monoamine oxidase
PDE	phosphodiesterase
RNA	ribonucleic acid

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