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REVIEW PAPER

Caffeine pouches: an emerging nicotine-free stimulant trend and its implications for public health

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Abstract

Oral caffeine pouches are a rapidly emerging nicotine-free stimulant product delivering caffeine through buccal absorption. Despite growing commercial availability and uptake among young people, peer-reviewed evidence on this product category remains extremely limited. This review aims to synthesize the available evidence on this product category and to assess whether a precautionary public health response may be warranted. Searches of PubMed, Scopus, and Google Scholar were supplemented by grey literature. Commercially available pouches contain 25-200 mg of caffeine per unit. Analogue evidence suggests buccal absorption may be faster than conventional oral ingestion. Biologically plausible risks from caffeine pharmacology and analogue products include cardiovascular stimulation, oral mucosal irritation, and acute caffeine toxicity, with adolescents and pregnant women at heightened risk. Caffeine pouches are classified as foods or dietary supplements in most jurisdictions, with no age-purchase restrictions or standardized dosing controls. In the absence of documented population-level harms, the rationale for early action rests on precautionary grounds: rapid market growth, high uncontrolled per-unit doses, and an established pattern of youth uptake of analogous oral pouch products. On this basis, coordinated regulatory oversight, dedicated empirical safety research, and targeted public health communication may be warranted before population-scale uptake.

Keywords: buccal administration, dietary supplements, caffeine, adolescent, public health

Introduction

Caffeine is the most widely consumed psychoactive substance in the world, with an estimated 69% of the United States population consuming at least one caffeinated beverage daily [1]. Traditionally delivered through beverages such as coffee, tea, and energy drinks, caffeine has in recent years appeared in an expanding range of novel delivery formats: chewing gums, dissolvable strips, oral sprays, and. most recently, oral pouches [2-4]. The latter – small sachets resembling nicotine pouches, placed between the lip and gum – represent a particularly significant development because they combine a potent stimulant with a buccal delivery mechanism that may accelerate systemic absorption beyond the rates achieved by conventional beverages [5].

The emergence of oral caffeine pouches cannot be separated from the broader context of the oral pouch market. The rapid rise of nicotine pouches, driven by brands such as ZYN, Velo, and on!, demonstrated that consumers would adopt tobacco- and smoke-free oral

stimulant formats at scale, including among adolescents [6,7]. Recent epidemiological data show that past-30-day nicotine pouch use among US 10th and 12th graders doubled between 2023 and 2024, from 1.3% to 2.6%, with co-use alongside e-cigarettes also increasing [8]. Manufacturers have observed this trajectory and moved to apply the same product architecture to caffeine, creating what is effectively a stimulant delivery device that sits in a regulatory and scientific grey zone [9]. Unlike nicotine pouches, which in the United States are now subject to the Food and Drug Administration (FDA) pre-market review as tobacco products [10], caffeine pouches are classified as foods or dietary supplements, a status that carries substantially fewer obligations regarding safety evidence, age restrictions, and marketing controls [11].

Part of the commercial appeal of caffeine pouches lies in features that set them apart from conventional caffeine sources: they require no liquid, preparation, or swallowing and can be used discreetly where coffee or energy drinks would be impractical [5]. Discretion, ease of concealment, and the ability to use the product where others are not permitted are also among the motivations most frequently reported by users of oral nicotine pouches [12]. Positioned as a nicotine-free alternative to products such as ZYN and a sugar-free alternative to energy drinks [11], they appear to have gained particular traction among younger users [13].

Simultaneously, the growth of social media platforms, particularly TikTok, as marketing channels may be contributing to awareness of caffeine pouches among demographic groups least equipped to make informed risk assessments (based on media reports, no systematic surveillance data currently exist) [11,13]. Recent emergency department surveillance found that caffeine-related visits among US adolescents aged 11-18 years more than doubled, albeit from a low baseline, between 2017 and 2023 [14], and a 2025 review of caffeine intoxication case reports identified minors in 21% of accidental exposures [15]. Caffeine pouches may represent an escalation of this risk due to their concentrated doses and rapid absorption kinetics.

Despite this trajectory, peer-reviewed evidence on oral caffeine pouches as a distinct product category is extremely limited. At the time of this review, only a single peer-reviewed study has investigated the effects of caffeine pouches directly: a 2026 crossover trial by Hulton et al. comparing an 80 mg caffeine pouch with caffeinated gum and placebo on physical performance outcomes. However, the study did not measure pharmacokinetic parameters [16]. No dedicated pharmacokinetic studies, epidemiological surveillance data, or comprehensive public health assessments of caffeine pouches have been published. This narrative review addresses this gap by synthesizing evidence on: (1) product characteristics and market

landscape; (2) pharmacokinetics and mechanism of buccal caffeine absorption; (3) health effects and vulnerable populations; and (4) the regulatory and public health policy landscape.

Aim of the work

The aim of this article was to synthesize the currently available evidence on oral caffeine pouches as an emerging product category and to assess whether, and in which areas, a precautionary public health response may be warranted, spanning regulatory oversight, empirical research, and clinical communication.

Methods

This research paper is a narrative review, prepared with reference to the Scale for the Assessment of Narrative Review Articles (SANRA) [17]. It was conducted to synthesize existing evidence on oral caffeine pouches and their potential public health implications. A literature search was conducted in PubMed, Scopus, and Google Scholar between February 2026 and May 2026. The following search terms and their combinations were used: “caffeine pouch”, “caffeine oral pouch”, “buccal caffeine”, “transmucosal caffeine”, “caffeine gum pharmacokinetics”, “oral nicotine pouch”, “energy product youth”, and “stimulant pouch”. Priority was given to publications from 2023 to 2026; selected seminal pharmacokinetic and pharmacological studies published earlier were retained where no contemporary equivalents exist. Sources were included if they addressed caffeine delivery via oral or buccal routes, health effects of concentrated caffeine products, oral pouch use behavior, or regulation of stimulant products. Publications were restricted to English-language sources. Sources were excluded if they were not available in English, did not concern caffeine or a relevant analogue product, or duplicated data were already reported in an included source. As only one identified study evaluated caffeine pouches directly, the majority of included sources concerned analogue products (caffeinated gum and oral sprays, oral nicotine pouches, and energy drinks) and were treated as indirect evidence. This distinction between direct and extrapolated evidence is maintained throughout the review.

As peer-reviewed literature on caffeine pouches is very limited, supplementation of grey literature was needed to create a bigger picture of the topic. Grey literature sources were identified through targeted searches of the websites of regulatory agencies (FDA, European Food Safety Authority (EFSA), Food Standards Agency (FSA), Food Standards Australia New

Zealand (FSANZ), and Health Canada), market-research reports, and publications from public health organizations, as well as through screening of the reference lists of included articles. These sources were used primarily for product, market, and regulatory information rather than for health-effect claims and are identified in the text as carrying a lower level of evidence. A total of 45 sources were included in this synthesis: 30 peer-reviewed articles and 15 grey literature sources. Evidence was organized thematically rather than pooled quantitatively. The source selection process is summarized in Figure 1.

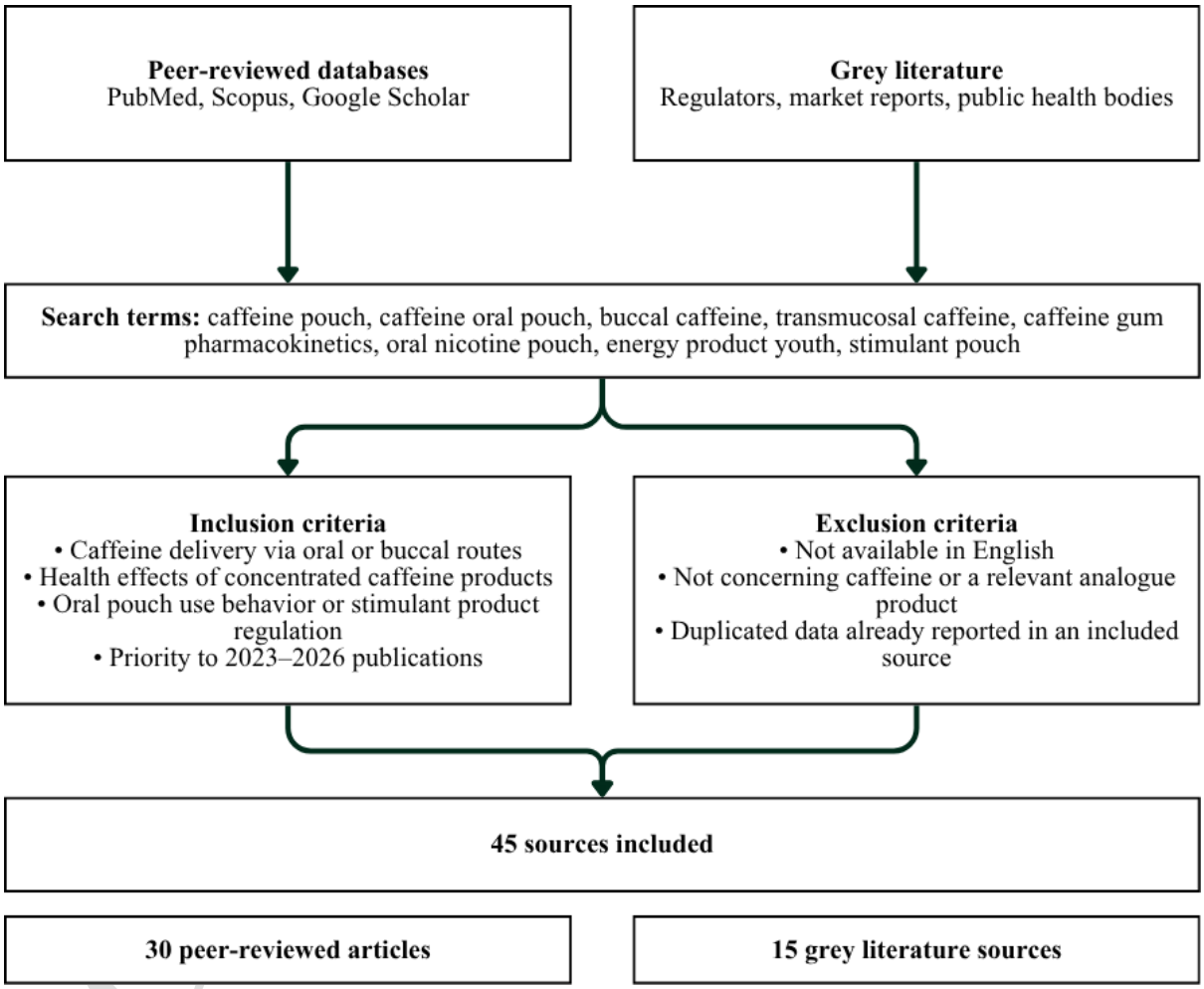

Figure 1. Source selection flowchart

Literature review results

Product characteristics and market landscape

Oral caffeine pouches are small, pre-portioned sachets made from plant-based fiber material filled with a blend of caffeine, fillers (commonly microcrystalline cellulose or plant fiber), flavorings, and pH-adjusting agents [9]. Users place the pouch between the upper lip and gum, typically for 15-30 minutes, during which caffeine is released and absorbed through the oral mucosa. The products do not require chewing, spitting, or swallowing, making them discreet – a characteristic that manufacturers have actively marketed [5]. Independent chemical analysis of oral pouches is limited. However, a screening study of 50 commercially available pouches, detected pharmacologically active additives, non-authorized flavorings, and substances exceeding food-safety intake limits, raising questions about the toxicological profile of pouch contents beyond their stated active ingredient alone (a study of oral nicotine pouches, used here as an indirect analogue) [18].

Caffeine content varies substantially across brands, from 25-50 mg in products positioned as “mild” options to 200 mg or more in “strong” variants, the latter equivalent to approximately two standard cups of coffee in a single pouch [13]. This concentration range is clinically meaningful: while 25-50 mg per use is unlikely to cause acute harm in healthy adults, repeated use throughout the day could readily exceed the FDA-recommended safe daily limit of 400 mg for adults, as well as the American Academy of Pediatrics’ recommendation that adolescents avoid caffeine altogether [19,20]. Table 1 summarizes selected commercially available products and their data sources. These data are derived entirely from manufacturers’ websites and have not been independently verified through chemical analysis.

Table 1. Comparison of selected commercially available caffeine pouch products [21-24]

Brand	Caffeine per pouch (mg)	Origin	Launched	Additional ingredients
GRINDS	25-100	USA	~2012	Coffee extract, B vitamins
Muse (Focus)	70	UK	2024	Flavorings, Alpha GPC, Theanine
Muse (Boost)	140	UK	2024	Flavorings, Alpha GPC, Theanine
Muse (Surge)	200	UK	2024	Flavorings, Alpha GPC, Theanine

Denssi	100	Finland	2024-2025	Flavorings
Nectr Energy	50	UK/US	2025	Flavorings

Notes: All the product characteristics shown are manufacturer-reported and have not been independently verified.

The global caffeine pouch market remains small but is growing rapidly. Based on market analysis (low-level evidence), the segment was estimated at approximately USD 71.3 million in 2025 and is projected to reach USD 107.2 million by 2032 [9]. The trajectory recalls that of nicotine pouches a decade earlier, though on a different metric: global retail sales of nicotine pouches reached 23.5 billion units in 2024, an increase of 50.5% over the previous year [7].

Pharmacokinetics and mechanism of buccal caffeine absorption

The pharmacological basis for the oral pouch format lies in the distinctive absorption characteristics of the buccal mucosa. Unlike the gastrointestinal tract, the oral mucosa is highly vascularized, thin, and accessible to small lipophilic and amphiphilic molecules – such as caffeine [25]. Molecules absorbed across the buccal mucosa enter the systemic circulation directly, without first passing through the gastrointestinal tract. For drugs with substantial first-pass metabolism, this can increase bioavailability; caffeine, however, already has near-complete oral bioavailability (~100%) and undergoes negligible first-pass metabolism [26], so any difference between the buccal and oral routes is likely to lie in the rate of absorption rather than the total amount absorbed. The application of buccal delivery to caffeine has been explored in chewing gum, sublingual sprays, and dissolvable strips. Recent reviews catalogued the emerging diversity of caffeine delivery formats and their implications [4,27].

Following conventional oral ingestion, caffeine is absorbed rapidly from the small intestine, with peak plasma concentrations typically achieved within 30-45 minutes post-ingestion [26]. Caffeine is eliminated primarily via cytochrome P450 1A2 (CYP1A2)-mediated hepatic metabolism, with an elimination half-life ranging from 2.7 to 9.9 hours depending on smoking status, pregnancy, medication use, and genetic polymorphisms [26].

Buccal delivery may alter this pharmacokinetic profile. Critically, at the time of this review, no dedicated pharmacokinetic study of caffeine pouches has been published in peer-

reviewed literature. The first and only peer-reviewed trial investigating caffeine pouches specifically was a randomized crossover comparison of an 80 mg pouch, 80 mg gum, and placebo in 19 participants. It was designed to assess physical performance outcomes; the authors specifically noted that the absorption rate for pouches has not been measured and was only inferred from buccal placement [16]. Pharmacokinetic data presented in this section are therefore derived from studies on caffeinated chewing gum and oral spray – products sharing buccal absorption as a delivery mechanism – and may not fully generalize to pouch-based systems given the differences in formulation, pH, and contact time. Seminal work by Kamimori et al. demonstrated that caffeine administered via gum was absorbed significantly faster than the same dose in capsule form, with buccal caffeine reaching detectable blood concentrations within 5 minutes and achieving plasma levels sufficient for early alertness or ergogenic effects by 15 minutes [28]. Caffeine's oral bioavailability is essentially complete (~100%) [26]; the relative bioavailabilities of approximately 64-77% reported for caffeinated gum reflect incomplete release of caffeine from the gum matrix rather than a limitation of buccal absorption itself [28]. Buccal delivery therefore offers no clear advantage in the total amount of caffeine absorbed, and any distinction lies in onset speed. Importantly, a 2025 randomized crossover study by McCarthy et al. of sublingual oral spray delivery (60 mg caffeine) found that buccal absorption did not accelerate the rise in serum caffeine concentration compared with caffeinated beverages, suggesting that absorption kinetics may depend strongly on formulation and contact time [29]. Pouch-based delivery, which involves prolonged mucosal contact (15-30 minutes), may behave differently.

Beyond pharmacokinetics, the Hulton et al. trial reported no statistically significant differences between pouch, gum, and placebo on muscular endurance, strength, or power, but effect-size analyses suggested small-to-moderate improvements in strength endurance and significant reductions in rating of perceived exertion (RPE) with the caffeine pouch versus placebo [16]. These results were insufficient to confirm ergogenic effects; the small-to-moderate effect sizes on secondary measures, in a trial of only 19 participants, are unstable and warrant replication in adequately powered studies before firm conclusions are drawn. Based on this indirect and partly conflicting evidence base, a 200 mg caffeine pouch may deliver a broadly comparable total systemic caffeine load to two cups of coffee, though potentially with a faster onset and sharper initial plasma concentration curve. This pharmacokinetic effect, if confirmed in dedicated pouch studies, may be associated with a greater likelihood of acute adverse effects such as palpitations, anxiety, and nausea, particularly at higher doses [30].

Health effects

Cardiovascular and neurological effects

Caffeine's primary mechanism of action is competitive antagonism of adenosine receptors, principally A1 and A2A subtypes, leading to increased neuronal firing, sympathetic nervous system activation, and catecholamine release [30]. As no cardiovascular studies of caffeine pouches exist, the evidence below is extrapolated from research on caffeine in sport and on energy drinks. At doses delivered by commercially available caffeine pouches (25-200 mg per unit), these effects may translate clinically to increased heart rate, elevated blood pressure, heightened alertness, and, at higher doses or in susceptible individuals, palpitations, tachyarrhythmias, and anxiety [2]. A 2022 systematic review of caffeine side effects in sport found that even standard ergogenic doses (3-6 mg/kg) increased the prevalence of adverse events, including tachycardia, palpitations, and sleep disruption, with higher doses producing more frequent and severe side effects [31]. A 2025 systematic review of the cardiovascular effects of energy drinks documented acute blood pressure rises, arrhythmias, endothelial dysfunction, and metabolic disturbances following caffeine-containing stimulant exposure, sometimes within 24 hours of a single can [32]. A 2024 worldwide meta-analysis found that energy-drink use among adolescents is already widespread. This provides an important baseline when considering any rise in the use of concentrated stimulant products such as caffeine pouches [33].

Acute caffeine toxicity may become a meaningful risk when dose stacking is considered. Users employing multiple pouches across a day may exceed the 400 mg daily limit recommended for healthy adults, with effects such as palpitations, anxiety, and disrupted sleep. Substantially higher intakes, well above any typical pattern of use, would be required to approach the doses associated with seizures or cardiac arrhythmias [2,30,34]. For context, the largest published case-report analysis of acute caffeine intoxication (216 cases, 1883-2023) found a median intoxicating dose of 12 g – equivalent to roughly 60 maximum-strength pouches – with seizures and wide-complex tachycardia associated with worse outcomes; 21% of accidental intoxications involved minors [15]. Recent emergency department surveillance further documents that caffeine-related emergency department visits among US adolescents aged 11-18 years more than doubled between 2017 and 2023, albeit from a low baseline [14].

Oral health

The oral effects of caffeine pouches remain largely unstudied. A single conference abstract examining one brand (GRINDS) reported cytotoxic effects on oral cells in vitro, but these preliminary findings have not been peer-reviewed [35]. Other findings from nicotine pouch research document gum recession and increased risk of periodontal disease with regular use [6,11,18]. The clinical significance of these findings for caffeine pouches has not been empirically studied. Evidence drawn from nicotine pouch research is indirect, as caffeine pouches do not contain nicotine or tobacco-specific nitrosamines – the main drivers of oral damage in traditional smokeless tobacco [36]. Nevertheless, the structural similarity in product format and the extended mucosal contact time (15-30 minutes per use, often repeated) provide a plausible basis for localized mucosal effects, but this requires confirmation in dedicated clinical studies.

Vulnerable populations

Adolescents represent the population of greatest concern. The developing brain is particularly sensitive to stimulant compounds, and the American Academy of Pediatrics recommends that children and adolescents limit or avoid caffeine entirely [19,34]. A 2025 cohort study (EDKAR) identified higher rates of cardiovascular risk behaviors among adolescents consuming caffeinated stimulant products four or more days per week at ≥ 3 mg caffeine per kg per day [37]. Given the documented rise in caffeine-related emergency department visits among adolescents [14] and the established pattern of oral pouch uptake in this age group [8], intentional caffeine pouch use among teenagers represents a plausible and concerning scenario, though dedicated epidemiological data are currently lacking.

Pregnant women represent a second high-risk group. Caffeine crosses the placenta and accumulates in fetal tissues, which lack CYP1A2-mediated clearance capacity. Observational studies have reported associations between caffeine intake below 200 mg/day and increased risks of fetal growth restriction and pregnancy loss, although causal interpretation is debated, partly because pregnancy-related nausea may reduce caffeine intake in viable pregnancies [38].

Individuals with anxiety disorders, cardiac arrhythmias, or hypertension are also at higher risk. These groups often take CYP1A2-inhibiting medications, including oral contraceptives, certain antidepressants, and quinolone antibiotics, which can substantially increase caffeine's effective half-life and systemic exposure [26].

Athletes, recreational gym-goers, and students represent additional high-exposure groups. Caffeine is widely used for ergogenic purposes in professional sport [39] and is present in most pre-workout supplements [40], while energy-drink use is prevalent among students seeking better academic performance [41], making the discreet, smoke-free pouch format a plausible vector for sustained use in these groups.

Regulatory and public health considerations

In the United States, caffeine pouches are classified as either dietary supplements or conventional foods, meaning they fall under the FDA food regulation rather than the more stringent tobacco product oversight that governs nicotine pouches [11]. Caffeine has been on the market since before 1994 and therefore qualifies as an "old dietary ingredient", meaning manufacturers may include it in supplements without pre-market notification to the FDA [42,43]. The practical implications are significant: there is no federal minimum purchase age for caffeine products, no mandatory pre-market safety review, and manufacturers are required to list caffeine as an ingredient but are not required to disclose its quantity on the label [42,43].

The regulatory path of nicotine pouches offers a useful comparison. The first FDA marketing authorization for nicotine pouches – ZYN brand – was issued in January 2025 after extensive regulatory review and was accompanied by strict restrictions on marketing to under-21s [10]. A recently published World Health Organization (WHO) report further warned that nicotine pouches are being aggressively marketed to young people [7]. No equivalent framework applies to caffeine pouches, creating a situation where a product with potentially comparable acute risk for young users faces minimal regulations.

European regulatory frameworks offer limited additional protection. Under the European Union (EU) food law, caffeine is permitted in foods and beverages without product-specific upper-dose limits for adults. The EFSA has established that single doses up to 200 mg and habitual intake up to 400 mg per day are safe for healthy adults, while flagging concern about consumption among children and adolescents, for whom a conservative level of 3 mg/kg body weight per day has been proposed [34]. EU Regulation No 1169/2011 requires that beverages exceeding 150 mg of caffeine per liter must have a warning label and disclose the exact caffeine content, but this labelling obligation does not extend to pouch formats classified as food supplements [44]. A recent regulatory analysis by Rinke et al. found that many high-caffeine supplements exceed the EFSA limits of 200 mg per dose and 400 mg per day. The authors also identified multiple Rapid Alert System for Food and Feed (RASFF) alerts,

including several classified as serious risk, highlighting a regulatory precedent directly relevant to high-dose caffeine pouches marketed as foods or supplements [45].

The United Kingdom, Australia, and Canada regulate caffeine pouches under general food or supplement legislation rather than as a distinct stimulant category. In the UK, caffeine-containing supplements fall under the FSA rules with no age-specific sales restrictions [46]. In Australia, the recent FSANZ reforms (P1056, 2026) introduce new controls on added caffeine in foods but do not directly address pouch products [47]. In Canada, caffeine pouches are classified either as foods or natural health products (NHPs), with age-related warnings applying only to high-caffeine NHPs [48,49]. Table 2 summarizes the regulatory status across key jurisdictions.

Table 2. Regulatory status of oral caffeine pouches and nicotine pouches across selected jurisdictions [42-44,46-49].

Jurisdiction	Caffeine pouch classification	Age restrictions (caffeine pouches)	Nicotine pouch classification	Key regulatory gap
USA	Food/dietary supplement (FDA)	None (federal)	Tobacco product (FDA)	No age gate; no pre-market safety review required; no mandatory caffeine disclosure
EU	General food law (EFSA oversight)	None (EU level)	Varies by member state	No specific pouch regulation; no mandatory dosing controls
UK	Food product/food supplement (FSA)	None	Regulated oral tobacco substitute	No age restrictions or marketing controls
Canada	Natural health product or food (Health Canada)	None	Tobacco and Vaping Products Act	No caffeine-specific pouch legislation
Australia	Food product (FSANZ)	None	Therapeutic goods or state law	Regulatory fragmentation; no pouch-specific controls

Notes: FDA – Food and Drug Administration; EFSA – European Food Safety Authority; FSA – Food Standards Agency; FSANZ – Food Standards Australia New Zealand.

The marketing dimension warrants attention. Systematic evidence on youth-targeted marketing of caffeine pouches is currently lacking. Available observations are from media reports and public health commentary rather than controlled surveillance data (low-level evidence) [11,13]. Based on these sources, caffeine pouch manufacturers appear to have adopted social media strategies with reach to young audiences. Products are gaining traction on platforms with predominantly young users. This gap between commercial practice and regulatory oversight warrants formal investigation.

Strengths and limitations

This review has several strengths. It provides the first comprehensive synthesis of available evidence on oral caffeine pouches as a distinct product category, covering product characteristics, pharmacokinetics, health risks, vulnerable populations, and regulatory status across multiple jurisdictions. Where possible, conclusions come from recent peer-reviewed literature on analogue products (nicotine pouches, caffeinated gum, energy drinks).

The principal limitations are: (1) peer-reviewed literature on caffeine pouches is extremely limited, with only one published trial focused on physical performance [16] and no dedicated pharmacokinetic, epidemiological, or clinical safety studies, necessitating substantial reliance on grey literature sources, including media reports, manufacturer websites, and market research reports, which carry low levels of scientific evidence; (2) pharmacokinetic conclusions are based on caffeinated gum and oral spray studies and may not fully generalize to pouch-based delivery systems, particularly given the divergent findings of Kamimori et al. [28] and McCarthy et al. [29]; (3) health effect conclusions are partly based on analogue evidence from nicotine pouch research; (4) no primary epidemiological data on caffeine pouch use prevalence exists in any population; and (5) the narrative design, while appropriate for an emerging topic, introduces selection bias that a systematic approach would avoid. These limitations are inherent to the early stage of the literature rather than avoidable methodological choices, and they define the research agenda rather than invalidate the review's contribution.

Conclusions

Oral caffeine pouches may combine several established public health risk factors into a single, under-regulated product category. They bring together the concentrated stimulant doses of energy drinks, a buccal delivery route whose absorption in pouches has not yet been

measured, the discreet and portable format of nicotine pouches, and the social-media marketing channels that have previously driven youth uptake of vaping and oral nicotine products. This convergence, however, rests on indirect evidence – analogue products, caffeine pharmacology, and a single direct study – rather than on dedicated research into caffeine pouches. The absence of dedicated empirical research and regulatory engagement on this topic reflects both the speed of the market emergence and the fragmented nature of regulatory frameworks that failed to anticipate it. If current use continues to grow, several precautionary measures may warrant consideration: age restrictions on purchase; mandatory dose labelling and pre-market safety review; limits on marketing in channels with large under-18 audiences; and clear public communication for parents, educators, and healthcare providers about identifying caffeine pouches, recognizing acute symptoms of caffeine toxicity, and the lack of standardized dose information. Future research should priorities dedicated pharmacokinetic studies of caffeine pouches, epidemiological data on adolescent use, clinical characterization of oral mucosal effects, and evaluation of potential regulatory interventions. Until peer-reviewed evidence is available, the conclusions of this review should be interpreted with appropriate caution given the indirect and grey literature evidence base on which they rest. Nonetheless, the precautionary principle in public health argues for proactive engagement with this emerging product category rather than waiting for population-level harm to appear.

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In the initial preparing of this manuscript, the author used Microsoft Copilot and Grammarly (Artificial Intelligence/AI) solely for language refinement, academic style enhancement, and text formatting. The tool assisted in improving clarity, coherence, and structural flow of the narrative, without generating scientific content or influencing the interpretation of evidence. All the conceptual work, data synthesis, argumentation, and conclusions were developed independently by the author. After using the tool, the author thoroughly reviewed and edited the entire manuscript and accepts full responsibility for its scientific content.

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