



Mainstream psychiatry reinstates therapeutic ventures of the remote past

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The reinstatement and revision of abandoned therapeutic ventures of the past has been an integral part of medical research and advancement. In psychiatry, much interest was generated recently by emerging data on the use of faecal supplements for restoring the neurochemical balance in the brain, and on the ingestion of placenta to stabilize neural circuits disrupted by childbirth-related hormonal changes. Herein, we consider the emerging scientific evidence and socio-cultural prerequisites favouring the re-entry of these heterodox customs, which are reminiscent of widespread instinctive behaviours in wildlife, into modern healthcare. We explore their evolutionary background and adaptive significance, and consider mechanisms of therapeutic benefits. Finally, we reflect on emerging opportunities and challenges, which present clues towards better prevention and treatment of major neuropsychiatric disorders.

Introduction

Influential works in ancient and early-modern pharmacy have included extensive debates and discussion of the use of human waste (e.g., blood, faeces, amniotic fluid and placenta) as remedies, to be ingested orally or applied topically for medical treatment [1–3] (Fig. 1). In the early days of pharmacy and drug discovery, radically innovative inorganic or synthetic drugs and remedies of other kinds were frequently critiqued for their lack of efficacy in comparison to the notional effectiveness of human waste. The renowned Englishman Robert Boyle, for instance, when comparing human excrements with chemical extracts or elixirs, stressed the nobility of the former. He prescribed *Zebethum Occidentale* (i.e., human dung) as a dried powder blown into the eyes as a treatment for blurry vision [4]. Interestingly, Boyle was cautious enough to warn 'not to use the waste of the mad as a remedy, lest one become mad oneself' [5].

It must be stressed that these early medical accounts were not without censor in their own time, with disparagement also being

widely documented. Still, the placenta and amniotic fluid have been considered of major relevance to the management of pain and distress related to childbirth. Numerous notes of caution against the ingestion of placenta or amniotic fluid can be found in the early pharmacy literature [6,7], indicating that afterbirth was a recognized remedial material that has been widely ingested for health benefits as well as for other purposes.

Although the adaptive role of these allegedly primeval and outwardly bizarre customs and their impact on the evolutionary fitness of humankind over millennia remains to be elucidated, the most parsimonious hypothesis explaining the prevalence of faeces and placenta ingestion in nature is that it provides a medical and nutritional advantage. Indeed, ingestion of dung (hetero- or auto-coprophy) is widely encountered in wild and domesticated animals, including all tested lagomorphs, rodents, cetartiodactyls, birds and carnivores, as well as primates, among which are our closest relatives, such as gorillas, orangutans and rhesus monkeys [8–10]. Likewise, post-parturition consumption of the placenta has been reported in the vast majority of mammals, with even some obligatory herbivores eating their afterbirth as well as other flesh

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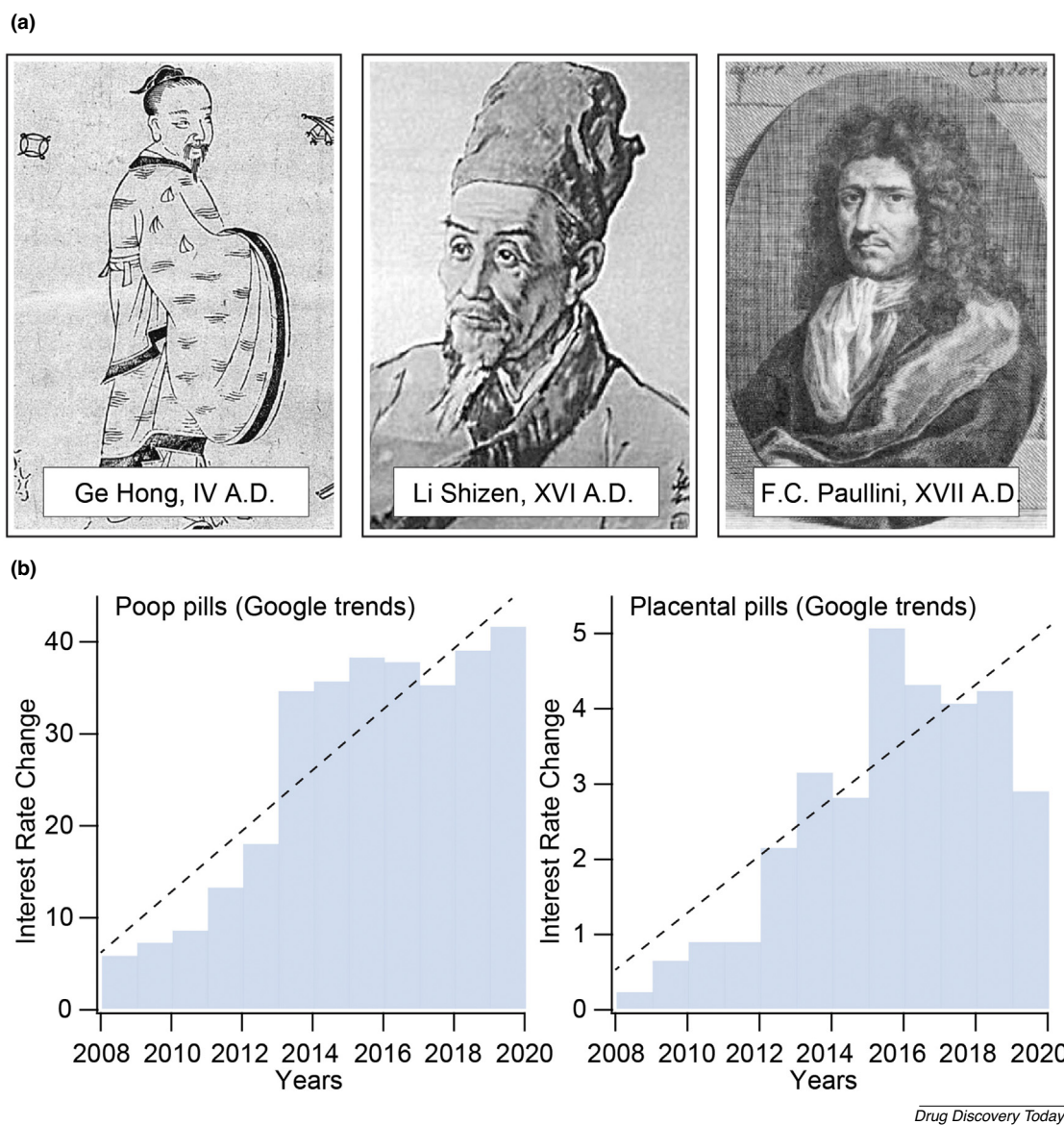


FIGURE 1

(a) Portraits of renowned proponents of the therapeutic use of human excrement. In ancient China, Ge Hong, author of the book *Zhou Hou Bei Ji Fang*, prescribed faecal transplant use for the treatment of food poisoning and typhoid fever. In early-modern China, Li Shizhen prescribed fermented, dried or fresh faeces for the treatment of abdominal disease, fever, pain and constipation. Early-modern German physician Franz Christian Paullini is the author of *Dreck Apotheke* (1696), the most comprehensive book on the medical use of human waste. Images courtesy of the Wellcome Collection. (b) Graphs presenting worldwide trends in Google searches for 'poop pills' (left) and 'placental pills' (right), revealing a remarkable rise of interest in these topics over recent years.

(i.e., liver, pork, and beef) immediately after delivery [11,12]. Owing to methodical and socio-cultural reasons, until recently, research into these exotic customs in humans was relatively scarce and was limited to studies of their impact on animal health and behaviour, confined to nutritional, immunological, protective and regenerative considerations within the framework of self-medication, either by learned behaviour or by intuitive zoopharmacognosy.

Nevertheless, there is increasing scientific evidence for the important homeostatic role of gut-brain interactions and the stimulating impact of the healthy gut microbiome on mental health and brain function. In addition, anecdotal accounts

emphasize the mind-stabilizing and antidepressant effects of placental hormones, which has implications for major neuropsychiatric diseases such as autism, post-partum depression and schizophrenia. These studies have led to a change in perception of instinctive coprophagy and placentophagy, and prompted more in-depth research into these long-outlawed customs. Emerging reports of the beneficial effects on mental health of microbiota transplants, whether through faecal infusion or via supplements containing gut microbiome or placental material, have fuelled in-depth analysis of the biology and neuromodulatory mechanisms underpinning the effects. Below, we consider the evolutionary and socio-cultural background and the alleged benefits of these

peculiar customs, and discuss their self-confident return to modern healthcare, along with the opportunities and challenges in harnessing them for the treatment of mental disorders.

Therapeutic reinstatement of microbiome transfer and placenta ingestion in psychiatry

When discussing complex animal behaviours, it is important to be mindful of their evolutionary benefits for the species, which might not always be clear [13,14]. Most primates, for example, ingest plants with strong antibacterial properties but with negligible nutritional value. Similarly, house sparrows add nicotine-rich cigarette butts to their nests to reduce mite infestation, without a clear role for enhancing the fitness of the species from an evolutionary point of view. Although these and similar behaviours seem to have medical benefits for individual animals, to qualify as a gain of species survival in a Darwinian sense, several criteria should be met, including the relevance to the natural inhabitants [13]. With the gradual move of *Homo sapiens* out from the natural environment over millennia, many primordial customs not only lost their adaptive value in terms of fitness gain but also became of dubious medical relevance, and at some stage even became tabooed by progressive human society. The resurgence of a general awareness and interest in natural medicine over recent decades not only fostered the widening use of traditional formulas and remedies of animal, herbal or mineral origin, but also manifested in a return of many bizarre and obnoxious practices and customs of the past, prohibited owing to their apparent conflict with accepted norms and values of society and cultural standards.

One of the most compelling examples of the return of ostensibly wierd customs is the rapidly expanding research into and use of human faecal formulas as a means of transplanting gut microbiomes. The therapeutic efficacy of this practice has been reported to exceed that of mainstream drug-based cures, with the treatment of *Clostridium difficile* infection using microbiome transplant [15] as the best-recognized example. This surge of research into gut microbiome restocking has helped to legitimize the use of faecal pills in traditional medicine: a centuries-old practice that has seemingly been abandoned for no good scientific reason. Indeed, from the time of the ancient Egyptians (circa 1550 BCE) to the late eighteenth century, faecal remedies had been an important part of European pharmacy, with excrements of different animals, including humans, being blended with other agents to produce medications that featured in standard apothecary lists [16]. Until recently, there was simply no place for the consideration that medical ingestion of excrement, *per se*, might be a sign of wrong-doing or madness; indeed, the use of faecal formulas and mixtures was widely agreed to be of prime medical relevance. The situation changed dramatically, however, in the nineteenth century, with the arrival of new ethnographic colonial imaginaries and especially after the discovery of primordial cultures in South East Asia and South America with their 'dirty habits'. Through a combination of fashionable thinking at the time and new theories of intestinal auto-intoxication, the long-established tradition of human excrement-based pharmacy began to be regarded as a remnant of primitive cultures that had failed to differentiate 'muck from what mattered' [3]. As a result, it became taboo, with doctors of the modern era losing interest in such remedies; in fact, the ingestion

of excrement in any form for self-medication became a sign of insanity.

Likewise, increasing interest in afterbirth consumption after parturition for its alleged psycho-stabilizing effects and other putative medical benefits marks the reappearance of another long-outlawed custom. Anthropological accounts suggest that the decisive reduction in routine human placentophagia occurred with the use of fire by *Homo erectus* almost two million years ago [17]. Nonetheless, the practice has been exercised widely in some communities and cultures over many millennia [17,18]. In Oriental and Western cultures, placentophagia is documented in ancient Egypt, with the practice disappearing from records with the arrival of Judeo-Christian traditions and loss of Paganism. In Eastern tradition, the consumption of the placenta for health reasons was used to treat a variety of conditions until the late middle ages, including arthritis, liver disorders, infertility and stimulation of the immune system, as well as milk production in childbearing women. In the modern scientific tradition, placentophagia has been documented since the early 1900s, with reports that the custom facilitated post-partum recovery and improved milk production [19]. This was followed by numerous accounts of maternal and non-maternal placental consumption in various communities and cultures in different parts of the world for nutritional, restorative and healing purposes [7,18]. The growing interest in the pursuance of a naturally healthy lifestyle has seen the practice of afterbirth ingestion reinstating itself in many countries and communities, with family members also occasionally partaking.

Considering the prosperous history of human waste usage for healthcare in the remote past, it is important and timely to reflect upon the extent to which the resurging trends of the medical use of human faeces and placenta are driven by an intuitive yearning for self-medication, retained from the evolutionary past, and the extent to which such trends are propelled by rapidly advancing scientific progress and evidence-based research. Dramatic changes in human ecology and lifestyle over the past century could have led to an impoverished gut microbiome through the use of disinfectants and excessive food processing. Without a doubt, limited exposure to natural microbiota might also have had a role in the growing numbers of issues related to the health of modern humans and could contribute towards the surge of interest in the practice of gut microbial inoculation. Likewise, with the nonchalant abandoning of placentophagy by humans in the recent past, the confident return of this custom might be also reflective of the intuitive self-medication drive triggered immediately after parturition, a drive aimed at getting through the hormonal, emotional and physiological impacts related to the challenges of late pregnancy and the delivery experience.

Role of microbiome restocking and placenta ingestion in mental health

The natural practice of excrement ingestion conceivably offers the most versatile means for microbiome restocking and constant enrichment in the wild. There is ample evidence showing that in many vertebrate lineages, coprophagy can provide an effective means for the exchange of microbes across generations. Both heterospecific coprophagy and allocoprophagy are considered as behaviours that inoculate the gut with bacteria and protozoa

[20–22]. Soave and Brand presented a detailed review of coprophagy in animals, with a description of a wide variety of related behaviours and discussion of their adaptive significance [9], extending from nutritional support to neurodevelopment and emotional bonding. The gut microbiome presents a key source for a constant supply of a wide range of vitamins, minerals, amino acids, trace elements and other nutrients. To maintain this essential source of goods, the microbiome needs constant exchange and replenishment. Prevention of coprophagia in lagomorphs, for instance, leads to rapid weight loss, particularly during the active growth phase, owing to a shortfall of nutrients [8,9]. Remarkably, rabbits have adapted a special ability to produce two types of faeces, soft and hard, with the former being rich in nutrients and being released at a specific time of the day. The consumption of faeces is also essential for normal growth in rodents, with its prevention slowing down their development. Likewise, the prevention of excrement consumption in rats causes nutrient and vitamin deficiency (in groups B and K) with serious health implications [23,24]. Ingestion of maternal faeces by pups has been implicated in developing suckling behaviour and bonding with the mother, as well as in transferring other behavioural phenotypes. Several mammals exhibit variations in microbiota composition that correlate with changes in odorant profiles [25]. Microbiome can also be predictive of age, sex and group differences [26]. Finally, the supply of biomaterials and metabolites, such as deoxycholic acid (DCA) and other bile acids, could have neuromodulator effects, promoting the maturation of the nervous system and nerve myelination [9] and neurogenesis [27]. Indeed, bile acids are widely present in the brain, with their levels falling significantly in demyelination diseases such as multiple sclerosis; DCA supplementation in an autoimmune encephalitis animal model has been shown to reduce inflammation and facilitate myelin recovery [28]. In primates and humans, accumulating preclinical and clinical data suggests a major role for gut microbiota in both somatic and mental health, with microbiota supplying the essential neuroprotective short-chain fatty acids n-butyrate and acetate, along with their metabolites [29].

Unlike the continuous supply of nutrients and metabolites by the gut microbiome, the benefits of placenta ingestion are strictly associated with childbirth. Among its potential benefits, analgesic and mood-stabilizing effects and emotional bonding are the most widely discussed, in addition to the nutritional impact and stimulation of milk production [7]. Although the underlying mechanisms of such effects remain unclear, emerging data from animal studies suggest specific molecular players.

The anti-nociceptive effects of placentophagy in animal studies, for instance, have been attributed to the release of endogenous opioids stimulated by the placental opioid-enhancing factor (POEF) [30]. It was argued that the ingestion of amniotic fluid might be more relevant for enhancing the pain threshold, as animals have access to amniotic fluid before delivery. The reduction of pain immediately after labour, in turn, facilitates maternal bonding and care.

The mood-stabilizer effects of placentophagy have been considered in relation to restoring hormonal balance after childbirth. In the medical literature, post-partum mood swings and psychosis have been viewed in close association with the acute withdrawal of oestrogens [31,32]. Despite a dramatic fall in the levels of several

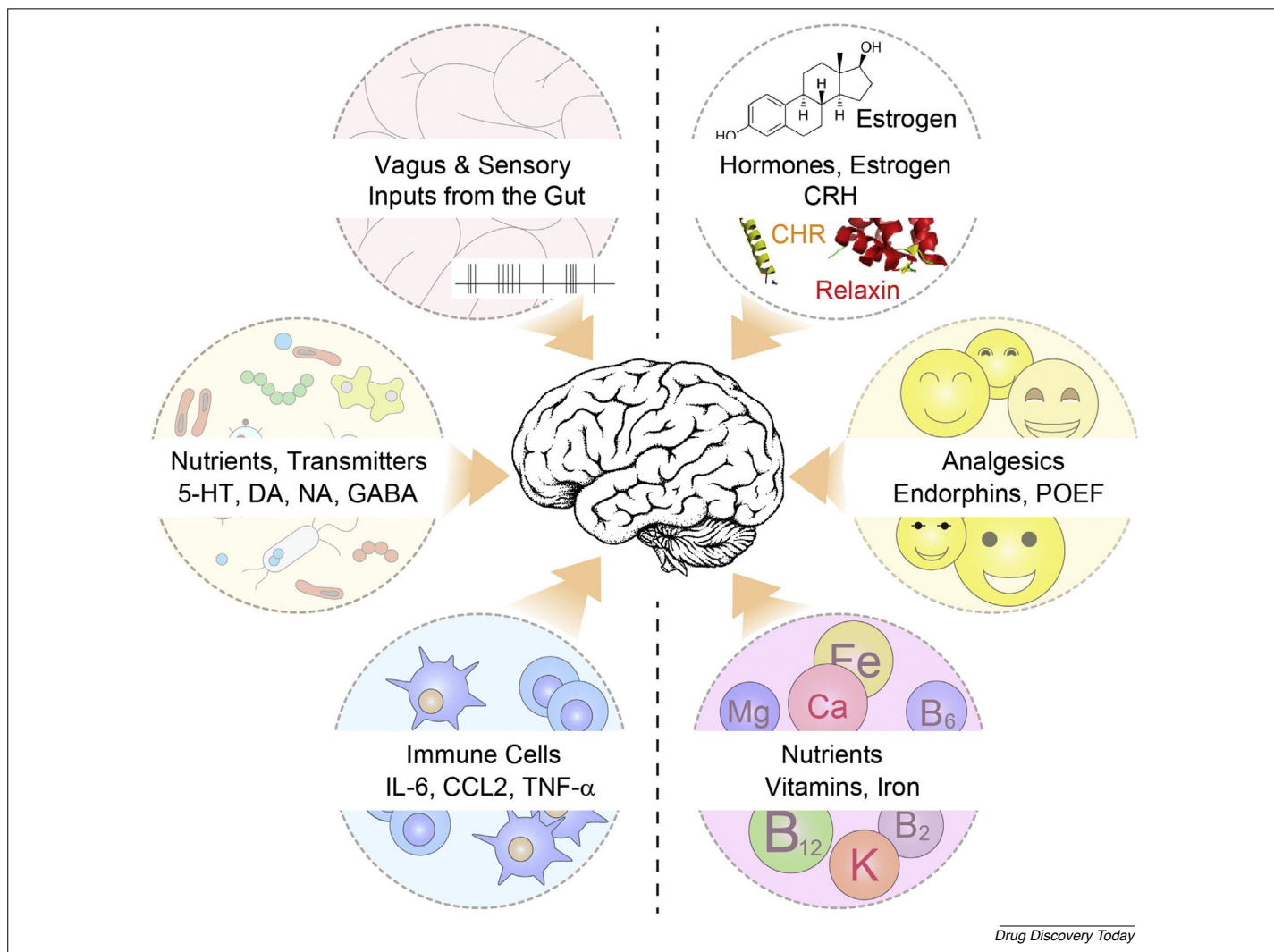
female hormones in the circulation after parturition, not all women show mood symptoms and psychotic experiences, leaving the matter open to debate and research. Because most research in this area has been carried out in animal models, consideration of the role of psycho-social factors related with childbirth, as well as other biochemical changes contributing to the pathobiology of post-partum depression in humans, is not feasible [33]. It is important to note, however, that the physiological drive towards the ingestion of placenta seems to be linked to specific hormonal and neural changes related to childbirth, which are thought to induce a particular type of post-partum hunger, rendering attractive the otherwise neutral or repelling smells and taste of placenta. This seems to be relevant to humans as well as obligatory herbivores, with the latter readily ingesting flesh only within a short time window after childbirth [11].

The re-entry of two outlawed prehistoric customs into modern society thus seems to have complex biological determinants, fortified by nutritional, hormonal and emotional rewards, as well as potentially other natural incentives. Conceivably, in the course of evolution, the circumstantial and constitutive supply of goods by the placenta and gut microbiome have organized complex and self-sustaining behaviours, warranting endurance and conservation of these customs. Emerging data, although partial and controversial, are in agreement with this interpretation, with major biological and nutritional factors propelling such trends, despite ill-disposed traditions and social norms, and leaving a decisive role to be played by research, which can bring clarity and a scientific basis for making informed decisions.

Neurobiological correlates and action mechanisms

At the core of any complex behaviour resides multi-part neural and humoral mechanisms. During development, communication between the gut and brain develops as a bidirectional process involving fast-acting neuronal and slow-acting hormonal factors. The ascending signals from the gut are largely mediated via vagal and dorsal root ganglion pathways, as well as by endocrine and immune mediators, whereas descending control goes via autonomic and enteric routes, as well as through the hypothalamic–pituitary–adrenal (HPA) axis (Fig. 2). Data from animal studies show that activation of vagal afferents by gut hormones and microbial signals, as well as mechanical stimuli, can induce significant neuro-behavioural changes, including enhanced circuit activity in brain stem structures, which, among other mechanisms, attenuates the stress response [29]. Selective vagal deafferentation in rats resulted in reduced anxiety behaviour, increased auditory fear response and related neurochemical changes within the limbic system [34,35].

The ascending humoral effects of the gut, in addition to hormones and peptides, can also be mediated via the release of small neuroactive substances such as 5-hydroxytryptamine, γ -aminobutyric acid, acetylcholine, dopamine and noradrenaline [36] or their precursors, specific to special bacterial strains. As part of the neurochemical mosaic of the brain, these active substances are involved in regulating the global dynamics of neural circuits as well as specific functional processes involved in the control of reward networks, mood, anxiety and arousal. In addition to influencing neural mechanisms and activity, the gut microbiome seems to regulate an array of housekeeping and homeostatic

**FIGURE 2**

Schematic representation of the mechanisms involved in the modulation of brain activity by gut microbiota (left) and ingested placenta (right). Left: multiple direct and indirect routes mediating gut microbiota effects on brain activity, with sensory and vagal afferents directly transmitting electrochemical signals (top), released nutrients and neuromodulators (middle), and immune cells releasing pro-inflammatory factors (bottom). Right: putative mediators of the psychoactive effects of placental ingestion after childbirth. Abbreviations: 5-HT, 5-hydroxytryptamine; CCL2, chemokine CC motif ligand 2; DA, dopamine; GABA, γ -aminobutyric acid; IL-6, interleukin-6; NA, norepinephrine; TNF- α , tumour necrosis factor- α .

processes in the brain, as well as immune responses. For instance, n-butyrate produced by gut microbiota is a potent stimulant of mitochondrial oxidation and gluconeogenesis, as well as an inhibitor of nuclear factor- κ B (NF- κ B) [37], with ameliorative effects in Parkinson's and Huntington's disease models [38]. The gut microbiota was also shown to influence the proliferation, maturation and function of numerous immune cells, as well as autoimmune processes driven by myelin-specific CD4⁺T cells, and dysbiosis and chronic inflammation implicated in psychiatric disorders [36].

Unlike the dual neuro-humoral effects of gut microbiota on brain functions, the effects of placenta ingestion on brain activity are mediated exclusively via humoral mechanisms, owing to the release of active substances into the circulatory system with modulator effects on neural processes (Fig. 2). Boosting the level of iron and vitamin B6 by placental ingestion after parturition is thought

to improve general energy levels and lower incidents of postnatal depression (PND) [39,40], with vitamin B6 proposed as a treatment option for PND. Although low levels of B vitamins have been viewed as risk factors for depression, it remains to be shown whether their increase in the circulation in relation to placental ingestion is sufficient for the alleged antidepressant effects. Among other placental factors that could potentially influence mental health, the restoration of corticotrophin-releasing hormone (CRH) and oestrogen activity has been considered. According to a study by the US National Institutes of Health, during the last trimester, there is a threefold increase in CRH in the blood, and its sharp fall at childbirth can trigger symptoms of depression. Similar to CRH deficit, acute oestrogen withdrawal might contribute to PND; a transdermal infusion of this hormone was reported to relieve the symptoms [7, HYPERLINK \l "Ref41" \o "[41] Coyle, C.W. *et al.* (2015) Placentophagy: therapeutic miracle or myth?

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Placenta consumption is also thought to decrease symptoms of PND via the replenishment of β -endorphins; however, no reliable differences in the levels of these hormones have been found in women with PND [42]. The placenta is rich in β -endorphins [41], but the concentration and activity of β -endorphins in processed and ingested placental tissue remain to be determined. Finally, the putative psycho-stabilizing effects of placentophagy could be secondary to its anti-nociceptive effects. Enhanced opioid-mediated analgesia by placental POEF, for instance, is expected to facilitate post-partum recovery and stimulate emotional bonding and maternal behaviour. The fact that the analgesic effects of POEF in animals are confined to a narrow time window after childbirth is in agreement with the specificity of such an effect with therapeutic potential, which nevertheless needs to be verified in humans.

Overall, although emerging scientific evidence and anecdotal data imply a complex neuro-humoral influence of microbiome transplants and placenta ingestion on mental health with a promising translational outlook, there is a pressing need for independent research to establish the mechanisms of action and to elucidate the medical benefits and safety margins for effective therapeutic translation. It should be stressed that the human placenta is currently treated by US federal law as medical waste, and should be handled accordingly [6]. Owing to the risks of bacterial contamination and toxic substances, before release the material must test negative for infectious disease, with signatures required by the patient and physician. At this stage, in addition to animal research, there is a major requirement for randomized clinical trials in humans to determine the true translational value of faecal transplants and afterbirth ingestion, if they are to qualify as a potential monotherapy or as part of a combinative treatment strategy.

Conclusions and outlook

One of the main prerogatives of modern medicine is its reliance on scientifically proven methods and manipulations. To qualify as a therapeutic in clinical trials, a potential lead should show relevance to at least one prevalent disease, offer effective and safe treatment, display adequate performance based on systematic evidence under a variety of settings, have a favourable cost-benefit ratio, possess desirable properties and be available as a single compound. Although some of these characteristics also pertain to traditional medicine, the principal difference between traditional medicine and science-based practice is that traditional remedies lack scientific backing in safety and efficacy, but are bolstered through the collective agreement and reinforcement of

established traditions that have passed the test of time. The growing therapeutic interest towards unorthodox and outwardly bizarre customs has sparked much debate and conflicting views. As reviewed throughout this study, both faeces and placental ingestion are exercised by the vast majority of mammalians, including our closest relatives, non-human primates. Although scientific research into these outwardly peculiar habits has been carried out so far mostly on animals, emerging data convey a simple yet important message that points towards their strong biological background in the history and evolutionary past of humans, possibly contributing towards the confident return of microbiome restocking and placental ingestion in modern medicine and society.

The upsurge of interest in these customs not only calls into question the tacit assumption that they have only been shifted into scientific focus as a result of the ever-expanding scope of systematic research, but also highlights the possible role of homopharmacognosy (i.e., the intuitive wisdom for self-medication and evolutionary memory) in the face of dramatic changes in human ecology and lifestyle. Both placental ingestion and gut microbiome restocking might have a variety of complex and beneficial influences on brain mechanisms and functions, ranging from invigorating nutritional and immunological impacts to emotional and psycho-stabilizing effects. It might well be that the favourable health effects of the discussed customs widely vary from species to species, and can be influenced by ecological and environmental conditions. Notwithstanding the conflicting views and a generally cautious and curious public perception, in-depth research into the therapeutic potential and underlying biology of these customs is now on the global medical agenda. As bizarre and enigmatic as the replenishing of human microbiome by faecal inoculation and placenta ingestion might appear, at their core these customs reflect an evolutionary continuity that tightly interconnects human biology, mental health and behaviour.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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