General Internal Medicine IX

Editor

Emre AYDIN

Dicle University

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PREFACE

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CONTENTS

Chapter 1 Popular Beverage Matcha Tea: Phenolic Compound Phytochemistry and Effects on Cognitive Function 1
Gülsüm DEVECI
Nilüfer ACAR TEK

Chapter 2 Tattoo Pigments and Carcinogenicity: Current Evidence and Controversies 19
Nurcan METİN

Chapter 3 An Investigation of Some Psychological Parameters of Obesity: Causes, and Adverse Outcomes 29
Aida SAHMUROVA
Mustafa Batuhan DEMİR

Chapter 4 ABO Blood Group: Medical Genetics 53
Yunus ARIKAN

Chapter 5 Current Biochemical Markers Involved in the Pathophysiology of Obesity, Metabolic Syndrome, and Insulin Resistance 77
Mustafa Metin DONMA

Chapter 6 The Blind Spot in Cancer Immunotherapy: Statistical Profile And Epidemiology of Immune-Related Organ Toxicities of Checkpoint Inhibitors 93
Şeyma YAŞAR
Neşe BAŞAK TÜRKMEN

Chapter 7 Infant Nurtition And Epigenetics Relation During the First Year of Life 111
Şule ARSLAN
Noor Mansoor Hasan Abdullah ALSUBARI

Chapter 8 The Role of Psychobiotics in Various Neurological Diseases 135
Suna KIZILYILDIRIM
Cansu ÖNLEN GÜNERI

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Chapter 1

POPULAR BEVERAGE MATCHA TEA: PHENOLIC COMPOUND PHYTOCHEMISTRY and EFFECTS ON COGNITIVE FUNCTION

Gülsüm DEVECİ[1]
Nilüfer ACAR TEK[2]

INTRODUCTION

Camellia sinensis, belonging to the *Theaceae* family, is a tea plant widely consumed worldwide [1]. Fermented herbal tea is obtained through different oxidation processes of these tea leaves, and this is the tea we consume [2]. Globally, three popular types of tea come from the same tea plant: green tea (unfermented), oolong tea (partially fermented), and black tea (fermented) [3, 4]. Each type of tea contains varying levels and significant amounts of compounds such as phenolic compounds, alkaloids (caffeine, theophylline, and theobromine), tearubigins, catechins, proanthocyanidins, theoflavin, flavonoids, volatile compounds, and organic acids [4-8].

Matcha tea, made from the *Camellia sinensis* plant, has recently become popular worldwide. Belonging to the green tea group, this type of tea is a powdered tea made from shade-grown *Camellia sinensis* leaves [9]. Looking at the marketing of matcha tea for 2024-2030, demand increased in 2023, with the largest share (53.1%) attributed to its use as tea [10]. Soubei, Aolǜ, Longjing, Zhaori, and Fenglǜ are different types of Matcha tea prepared from the *Camellia sinensis* plant [11]. Matcha's raw material is called *Tencha*. Different subspecies of the *Camellia sinensis* plant (*Camellia sinensis cv. Yabukita, Camellia sinensis cv. Longjing,* and *Camellia sinensis cv. Baiye*) are three different types of tea plants from which *Tencha*, the original form of Matcha tea, is obtained [12]. Matcha is obtained

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conditions. Additionally, theanine content, which is important for anxiety, stress, and cognitive function, should be analyzed using similar methods. These analyses should also examine the levels of caffeine and epigallocatechin gallate, which may be antagonists, and their interactions with each other.

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Chapter 2

TATTOO PIGMENTS AND CARCINOGENICITY: CURRENT EVIDENCE AND CONTROVERSIES

Nurcan METİN[1]

INTRODUCTION

Tattooing is the process of placing permanent pigments into the dermis for cosmetic or medical purposes. Includes decorative tattoos, permanent makeup, and medical tattooing (1). In recent years, tattoos have become increasingly popular in developed countries, especially among adolescents and young adults (1). Since tattoos are often applied at a young age and remain in the skin for many years, individuals may have long-term exposure to the chemical substances found in tattoo inks. Although tattoos are generally considered safe, concerns have been raised about the possible long-term effects of these substances and the need for appropriate safety regulations (1,2). In particular, population-based studies examining the possible relationship between tattoos and cancer are still limited (2).

TATTOO PIGMENTS AND THEIR COMPONENTS

Tattoo inks are mainly composed of pigments, solvents, stabilizers, and other additives (2) (Table 1). Pigments account for approximately 25–60% of the ink formulation. Organic pigments, especially azo dyes, are commonly used because they provide bright and stable colors. However, some azo pigments may break down into primary aromatic amines (PAAs), several of which have carcinogenic properties. Carbon black, the main pigment used in black tattoo inks, is produced by incomplete combustion of petroleum-based materials. It may contain polycyclic aromatic hydrocarbons (PAHs), including benzo[a]pyrene and dibenzo[a,h]anthracene, which are classified as Group 1 carcinogens by the International Agency for Research on Cancer (IARC) (3,4). N-nitrosamines, such as N-nitrosodiethanolamine and nitrosodimethylamine, may also occur as impurities in tattoo inks. Many N-nitrosamines have shown carcinogenic effects even at low concentrations in animal studies (5).

pigments, and identify individuals who may be at higher risk. Such data are needed to better understand the long-term safety of tattooing and to guide future public health recommendations.

Table 3. Cases of malignant and benign skin tumors occurring in tattooed skin

Tumor Type/Cases	Gender	Age	Location
Melanoma: 43 cases, (1938-2022)	Men 81.4% (35) Women 7% (3) Unknown 11.6% (5)	46 (9-82) 41 (34-54)	Face (1) Chest (4) Abdomen (2) Back (7) Arm (22) Leg (3) Unknown (4)
Basal Cell Carcinoma: 40 cases, (1976-2023)	Male 35% (14) Female 25% (10) Unknown 40% (16)	54 (40-66) 49 (28-72) 35	Face (6) Back (10) Arm (9) Unknown (15)
Squamous Cell Carcinoma: 20 cases, (1966-2022)	Men 50% (10) Women 40% (8) Unknown 10% (2)	50 (35-79) 50 (24-74)	Face (2) Back (10) Arm (8) Leg (7) Unknown (4)
Keratoacanthoma: 48 cases, (1973-2021)	Male 44.8% (26) Female 33.3% (16) Unknown 10.3% (6)	49 (24-70) 46 (24-65)	Face (1) Back (1) Arm (14) Leg (25) Unknown (7)
DFSP: 4 cases, (2005-2020)	Men 50% (2) Women 50% (2)	44 (35-52) 33 (29-37)	Back (2) Arm (2)
Dermatomyofibroma: 1 case, (2013)	Man		Chest
Leiomyosarcoma: 1 case, (2008)	Man		Arm
Desmoplastic Spitz nevus: 1 case, (2018)	Woman		Arm
NHL: 1 case, (1978)	Man		Arm
B-cell lymphoma: 1 case, (1992)	Man		Arm

DFSP: Dermatofibrosarcoma Protuberans; NHL: Non-Hodgkin Lymphoma.

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Chapter 3

AN INVESTIGATION OF SOME PSYCHOLOGICAL PARAMETERS OF OBESITY: CAUSES, AND ADVERSE OUTCOMES

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1. INTRODUCTION

Obesity is a global health problem that threaten individuals' life and defined as a long-term inequality between calory intake and spent energy in a day (1, 2). Body mass index (BMI) which is calculated as individual's weight (counted as kg) is divided by square of height (calculated as m) of the individual (as kg/m^2). Overweight is defined as having between the BMI of 25-29.9 kg/m^2, and obesity is defined as having more than the BMI of 30 kg/m^2 (3,4,5,6). In the human history, depending on the culture, an excess body size has been seen as the representative of prosperity, richness, greater social status, and well health; however, its adverse outcomes for health were cumulatively explored since 20^{th} century (7). Obesity and overweight prevalence have increased since 1980 (8). Obesity has a negative outcome of physiological functions of patients presenting crucial public health troubles increasing the risk of such disease conditions, for instance, diabetes mellitus, various types of cancers, cardiovascular disease, and musculoskeletal disorders; besides physiological consequences of obesity, its psychological background is also more profound (9, 10). Obesity, over the years, has been several times associated with psychological problems, for example, depression, anxiety, stress, low self-esteem, suicide thoughts, and quality of life (11, 12, 13). A study conducted by Pereira-Miranda et al. (2017) found that individuals with obesity are at risk of depression 32% more than those who have not obesity (14). The other study which was conducted by Gariepy, Nitka, and Schmitz (2010)

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rapidly, shortened breaths, have negative psychosocial outcomes, social isolation, loneliness, or discrimination causing lack of satisfaction individual's own life. Due to such problems, people may avoid of being social; workplace discrimination, academic place harassment cause individuals to have such problems, for instance, low academic performance, unemployed, or being single. All the consequences, when they are considered, including social beauty norms, may contribute to development of many psychological problems. All of the experiences that were mentioned enhance body dissatisfaction, internalized shame, social withdrawal, and loneliness causing risk factor for depression, anxiety, or eating disorders.

7. SUGGESTIONS AND FUTURE DIRECTIONS

Based on the relationship between obesity and investigated psychological parameters that cause obesity, or caused by obesity carry an important role for public health. First of all, education for society is crucial to understand significance of the relationship. After that, routine psychological screen for individuals who carry risk of such psychological disorders that cause obesity, for example, depression, eating disorders, or chronic stress. Environmental variables that cause obesity bidirectionally should also work with people who suffers from, so to speak, loneliness, social isolation, stigmatization, or such traumas, for instance, physical or psychological abuse. Cognitive Behavioral Therapy (CBT), for instance, may be thought to be an effective interpretation to work on self-worth, perceived stress, or changing maladaptive behaviors. Education, or campaigns, in schools or work places, may also work on weight-related stigmatization, bullying, or teasing. For future studies, longitudinal studies should be conducted to analyze different mental problems that cause obesity, or caused by obesity. These longitudinal studies may work on, furthermore, development of psychological interpretation techniques. Neurological pathways also should be worked on obese people, or people who are at risk of developing obesity.

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Chapter 4

ABO BLOOD GROUP: MEDICAL GENETICS

Yunus ARIKAN[1]

1. INTRODUCTION

The recognition that human blood is not universally compatible emerged from fatal reactions during blood transfusion attempts in the late nineteenth century (1). However, a systematic explanation of this incompatibility did not become possible until the groundbreaking work of Karl Landsteiner in 1900. By mixing serum and erythrocytes obtained from different individuals, Landsteiner observed that some sera agglutinated the erythrocytes of certain individuals, whereas others did not (2). These observations demonstrated that human blood possesses distinct antigenic characteristics and led to the identification of three major blood groups, designated A, B, and O. For this discovery, Landsteiner was awarded the Nobel Prize in Physiology or Medicine in 1930 (3). Landsteiner's discovery revolutionized the practice of blood transfusion. Recognition of the need for compatibility between donor and recipient blood groups made transfusion considerably safer and has since contributed to saving millions of lives. Today, the ABO system remains a cornerstone of transfusion medicine and is also important in organ transplantation, forensic medicine, paternity testing, and disease susceptibility studies.

2. MOLECULAR BASIS OF ABO SYSTEM

2.1. ABO Gene Organization

The *ABO* gene (OMIM entry 110300), the primary genetic determinant of the ABO blood group system, is located on the long arm of human chromosome 9 at 9q34.1–q34.2. It spans approximately 18–20 kb and consists of seven exons. The contribution of these exons to the coding sequence is unequal, with most of the

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all variants on a chromosome to be viewed together and the haplotype to be determined directly. TGS also offers advantages in detecting recombination events and characterizing repetitive regions.

ABO genotyping complements serological testing when insufficient, especially in weak subgroups and transplantation. Serological methods remain primary for routine screening, but NGS and TGS use will grow as costs fall, particularly for rare blood group banks and precision transfusion.

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Chapter 5

CURRENT BIOCHEMICAL MARKERS INVOLVED IN THE PATHOPHYSIOLOGY OF OBESITY, METABOLIC SYNDROME, AND INSULIN RESISTANCE

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INTRODUCTION:

Obesity is a critical health problem with a rapidly increasing prevalence and has become a global public health threat. Adult obesity, the foundations of which are established during childhood, substantially increases the risk of numerous chronic diseases, particularly type 2 diabetes mellitus (T2DM), metabolic syndrome (MetS), cardiovascular disorders (CVDs), and various malignancies (1).

In addition to the early diagnosis of obesity, which is associated with numerous life-threatening chronic diseases in adulthood, and the implementation of necessary preventive measures, the evaluation of effective and current biochemical markers that may be associated with potential mechanisms underlying obesity is an important and significant area of scientific research, particularly with the aim of preventing the development of obesity and its possible complications (2).

In this article, current and effective biomarkers that are thought to be associated with the diverse and complex mechanisms and interactions involving obesity and adipose tissue are reviewed in light of the current literature. The general characteristics of the following current and effective biomarkers, as well as their roles in the pathophysiology of obesity, were investigated and evaluated: PPARGC1A (peroxisome proliferator-activated receptor gamma coactivator 1-alpha [PGC-1α]), cMyBP-C (cardiac myosin-binding protein-C), chemerin, LBP (serum lipopolysaccharide-binding protein), CgA (chromogranin-A),

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differentiation. Circulating CTRP9 concentrations are significantly decreased in patients with coronary atherosclerosis (78,79).

XXIII. MTRNL (Meteorin-Like Protein):

Metrnl is expressed in skeletal muscle, cardiac tissue, and adipose tissue and has beneficial functions in insulin resistance, obesity, and inflammation. MTRNL has been shown to provide protection against cardiac hypertrophy and doxorubicin-induced cardiotoxicity (80). Given its known metabolic and anti-inflammatory properties, MTRNL, as an exercise-induced myokine, is considered a mediator of the beneficial effects of exercise in ameliorating obesity-related complications such as insulin resistance, T2DM, and inflammation (81).

CONCLUSION:

In this article, current biochemical markers involved in the pathophysiology of obesity, metabolic syndrome, and insulin resistance were reviewed. In addition to the well-established and reliable biomarkers whose effectiveness has been demonstrated on international scientific platforms, namely hs-CRP, adiponectin, leptin, and ghrelin, a detailed analysis of the current literature and an examination of the molecular mechanisms through which these biomarkers exert their effects in obesity indicate that lipocalin and LBP, in particular, as well as progranulin, neudesin, and preptin, play active roles in the pathophysiology of obesity. These biomarkers should therefore also be considered important biomarkers in the assessment and prevention of obesity, metabolic syndrome, and insulin resistance.

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Chapter 6

THE BLIND SPOT IN CANCER IMMUNOTHERAPY: STATISTICAL PROFILE AND EPIDEMIOLOGY OF IMMUNE-RELATED ORGAN TOXICITIES OF CHECKPOINT INHIBITORS

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1. INTRODUCTION

Immune checkpoint inhibitors (ICIs) are monoclonal antibodies that reactivate the antitumour T-cell response by blocking the inhibitory signals that malignant cells exploit to evade the immune system. Agents targeting the programmed cell death protein-1 (PD-1), programmed cell death ligand-1 (PD-L1), cytotoxic T-lymphocyte-associated protein-4 (CTLA-4) and, more recently, lymphocyte activation gene-3 (LAG-3) axes have changed survival outcomes in melanoma, lung cancer, renal cell carcinoma, head and neck cancers, urothelial cancers and numerous other solid tumours (Brahmer et al., 2021).

The principal safety issue accompanying this clinical success is a toxicity spectrum that is biologically distinct from that of conventional cytotoxic therapies. Because ICIs can weaken peripheral tolerance mechanisms, they may cause immune-related adverse events (irAEs) in virtually any organ, including the skin, gastrointestinal tract, endocrine organs, lungs, liver, kidneys, heart, nervous system and musculoskeletal system. The SITC guideline reports that the incidence of any-grade irAEs is approximately 74% and that of grade ≥3 events 14% with anti-PD-(L)1 therapies; 89% and 34%, respectively, with anti-CTLA-4 therapies; and approximately 90% and 55% with combination ICI therapy (Brahmer et al., 2021).

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by showing not only who is at high risk but also which variables drive the risk prediction (Lundberg & Lee, 2017; Collins et al., 2024).

11. CONCLUSION

While immune checkpoint inhibitors represent one of the most important therapeutic transformations in modern oncology, immune-related organ toxicities are the principal safety cost of this success. The toxicity spectrum extends from frequent and mild dermatological/endocrine events to rare but highly fatal myocarditis and neuromuscular overlap syndromes (Brahmer et al., 2021; Nielsen et al., 2024).

No single data source is sufficient for epidemiological assessment. Clinical trials play a complementary role for incidence, real-world cohorts for risk factors and long-term outcomes, and pharmacovigilance systems for rare safety signals. RR, OR, HR, ROR, PRR, IC, EBGM, meta-analysis and time-to-event methods answer different questions and should not be used interchangeably (Bate & Evans, 2009; Reynolds et al., 2021).

The most accurate risk profile is one that combines the questions 'how frequent?', 'how severe?', 'when does it occur?', 'is it permanent?' and 'in which patient is it more likely?' within a single framework. As ICI use expands into early-stage and long-surviving cancer populations, this perspective—shifting from acute irAEs towards chronic toxicity and lifelong organ sequelae—will be one of the key agendas of clinical research and pharmacovigilance in the coming years (Patrinely et al., 2021; Johnson et al., 2022).

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Chapter 7

INFANT NURTITION and EPIGENETICS RELATION DURING THE FIRST YEAR OF LIFE

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INTRODUCTION

Early development represents a period in which environmental exposure can have consequences that extend beyond childhood. This development stage begins during pregnancy and continues into early childhood. Nutritional exposures, smoking, endocrine-disrupting chemicals, and psychological and biological stressors may affect development during this period (Godfrey et al., 2025). These observations from the basis of the *Developmental Origins of Health and Disease (DOHaD)* concept, which links conditions during early development with health outcomes later in life (Godfrey et al., 2010). Early epidemiological findings, including the relationship between lower birth weight and later cardiovascular mortality, contributed to the development of this concept (Barker & Osmond, 1986).

Nutrition is an essential environmental factor during these sensitive developmental periods. Much of the available research has widely examined nutritional exposure during pregnancy and its influence on fetal development and subsequent health through epigenetic modifications. However, epigenetic programming does not end at birth. The early postnatal period also remains sensitive to nutritional exposures, including breastfeeding and complementary feeding (Koemel & Skilton, 2022).

The epigenome shows considerable plasticity during early development, making it responsive to environmental and nutritional exposures. Epigenetic

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Chapter 8

THE ROLE OF PSYCHOBIOTICS IN VARIOUS NEUROLOGICAL DISEASES

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INTRODUCTION

With the rapid aging of the global population, neurological diseases (NDs) are expected to become the second leading cause of mortality worldwide, posing a major threat to human health and quality of life (1). Despite substantial research efforts, the exact causes and underlying mechanisms of NDs remain poorly understood, and currently available treatment options remain limited (2). Discovering new mechanisms or alternative factors that may affect the development or therapeutic strategies for these diseases is of great interest.

One such factor is the gut-brain axis, which encompasses the neurological, immunological, endocrine, and metabolic pathways that enable two-way communication between the gut and the brain (2-6). NDs are often associated with aberrant gut microbiota composition (2).

The term "gut microbiota" refers to the diverse community of commensal microorganisms residing in the gastrointestinal tract, including bacteria, fungi, viruses, archaea, and protozoa that live in symbiosis with the human host (7). The gut microbiota communicate with the central nervous system (CNS) through the enteric nervous system (ENS). This interaction is proposed to be mediated by neuroactive compounds, gut hormones, peptides, and microbial metabolites that reach the brain via the immune system, circulatory pathways, or the vagus nerve, thereby maintaining physiological balance. The nervous system then controls gut motility and homeostasis. This bidirectional interaction causes behavioral and

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