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CHRONOPHARMACOLOGY AND TREATMENT OF CANCER THROUGH CHRONOTHERAPY

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ABSTRACT

All living things, including humans, undergo regular changes in their physiological, biochemical, and behavioural states. These variations prioritize specific bodily activities at specific times of the day while conserving energy at other times in order to maximize energy utilization. The central and peripheral circadian clocks regulate circadian rhythm in response to zeitgebers like food and sunlight. Chronopharmacology is the study of how medications are influenced by biological rhythms. It aims to improve drug therapy by choosing the right moment to provide pharmaceuticals for optimum effectiveness and fewest side effects. Cancer chronotherapy seeks to enhance the tolerance and effectiveness of anticancer medications by administering them in accordance with circadian rhythms. Nevertheless, research on mice and human subjects demonstrates that lifestyle factors such as sex, genetics, pharmaceuticals, and cancer may alter the dynamics of the host's metabolic pathways and circadian clocks, affecting when it is best to provide medications. In fact, the mathematical modelling of chronopharmacology may help to modify the ideal time in light of patient-specific factors. Irinotecan is a topoisomerase I inhibitor with a complicated metabolism and a history of effectiveness against colorectal cancer. Here, we use in vitro and in silico approaches to define the key molecular pathways that control the chronopharmacology of irinotecan. According to in vitro circadian medication timing, these molecular rhythms translated into statistically significant alterations in pharmacokinetics and pharmacodynamics. According to the time of the medication, the top-up of the several coordinated chronopharmacology pathways caused a four-fold variation in irinotecan-induced apoptosis. Cancer and other diseases have been linked to circadian abnormalities.

KEYWORDS: Chronopharmacology, Chronopathology, Chronophysiology, Chronopharmacokinetics, Chronoesthesy, Chrono-Pharmacotherpy, Biological Rhythm, Cancer.

INTRODUCTION

Like other mammals, humans exhibit notable rhythmic fluctuations in a variety of biological processes. Chronobiology is the branch of biology that studies how living things cycle through different biological rhythms and how they adapt to those rhythms. Biorhythms come in a variety of forms, including circadian, ultradian, infradian, circaseptan, circalunar, and circannual.[1]

Biorhythms	cycle length
circadian	Around 24-hour cycle
ultradian	Around 24-hour cycle
infradian	Around 24-hour cycle
circaseptan	Around 7 days cycle
circalunar	cycle length corresponds with the lunar cycle (approximately29.5 days).
circannual	Around 1 year cycle

Circadian rhythm

Many physiological functions in humans are regulated by the circadian rhythm. The Latin words "circa," which means "around," and "diem," which means "day," are combined to get the English word "circadian." The central and periphery clocks regulate the circadian rhythm. Its control also involves the hypothalamo-pituitary-adrenal (HPA) axis and melatonin.[2]

Role of circadian clocks

A large portion of our body's cells have circadian clocks. Maximizing metabolism and energy consumption for sustaining an organism's essential processes is the main objective of the circadian clock. They use the 24-hour cycle to control homeostatic processes like the sleep-wake cycle, appetite, hormone levels, and other body functions. Circadian clocks are divided into slave/peripheral clocks, which are found in all other body cells, and master/central clocks, which are found in the suprachiasmatic nucleus (SCN) of the anterior hypothalamus. The central clock, which is organised hierarchically, controls the outlying clocks. The molecular oscillators in both clocks are governed by zeitgebers, or outside stimuli. The zeitgebers range from light to food to exercise, among other things. Different environmental cues called zeitgebers synchronise the central and peripheral clocks.[3]

Types of circadian clocks

1) Central clock: A central clock is housed in the hypothalamic suprachiasmatic nucleus (SCN).
2) Peripheral clocks: All other cells have peripheral clocks.

The suprachiasmatic nucleus (SCN), the central clock, communicates with the peripheral clocks directly and indirectly.

- The hypothalamo-pituitary-adrenal (HPA) axis and autonomic nervous system activation are two examples of neuronal and hormonal signals that are sent directly from the SCN to peripheral clocks.
- Body temperature variations and feeding habits are indirect signals sent by the SCN to the peripheral clocks.

Sunlight serves as the central clock's primary timekeeper. Once sunlight reaches the retina, the retinohypothalamic tract transmits the signal to the SCN. The SCN sends both direct and indirect signals that regulate the peripheral clocks. The direct signals are provided via hormonal signalling and neural networks (e.g., cortisol). The SCN modifies body temperature and eating habits in order to send indirect signals to the peripheral clocks. The SCN modifies body temperature and eating habits to send veiled signals to the peripheral clocks. Changes in body temperature and eating patterns are indirect cues that the SCN relays to the peripheral clocks. The circadian rhythm is regulated by a number of transcription factors. The crucial transcription factors are BMAL1, NPAS2, and CLOCK.[5]

Chronopharmacology

The study of a drug's biological rhythm dependencies with relation to its pharmacological effects and/or pharmacokinetics/dynamics in both humans and animals is known as chronopharmacology.[6,7]

Various aspects of chronopharmacology

1) Chronokinetics

The study of predicted rhythmic fluctuations in drug pharmacokinetic characteristics is known as chronopharmacokinetics. As a result, pharmacokinetic characteristics such drug absorption, distribution, metabolism, and excretion exhibit circadian fluctuations. To optimise pharmacological therapy, time of drug delivery can be determined using chronopharmacokinetic data.

- **Absorption's circadian rhythms**

Circadian factors, such as stomach motility, gastric acid secretion, and gastrointestinal blood flow gastric emptying time, affects drug absorption and bioavailability. Due to a stronger blood supply to the gastrointestinal system in the morning and a quicker stomach emptying time, most lipophilic medicines are more efficiently absorbed in the morning than in the evening.[6,7]

- **Distribution's circadian rhythms**

The distribution of a medicine is influenced by factors such as protein binding, membrane permeability, blood flow, body size, and composition, with blood flow and protein binding exhibiting the greatest circadian variation. The autonomic nervous system regulates blood flow, with the sympathetic nervous system having a stronger nocturnal influence. Since sympathetic activity is more prominent during the day and less prevalent at night, daytime blood flow is greater than nighttime blood flow. Because of the circadian cycle of the liver changes throughout the day and night, the amount of plasma proteins it makes, such as albumin and globulin, varies. Their blood levels start off relatively low in the evening, rise during the day and then peak in the late afternoon.[6,7]

- **Circadian rhythms in metabolism**

Drug metabolism in the liver depends on the activity of metabolizing enzymes & hepatic blood flows, which are changes during the day. The circadian rhythm controls every stage of drug metabolism. Hepatic blood flow changes have a circadian impact on the metabolism of medications like propranolol. Microsomal oxidation processes are most active during the day and least active at night. Enzymes with and without microsomes exhibit circadian oscillations. Sulphate conjugation reactions, on the other hand, happen far more swiftly at night than they do during the day.[6,7]

- **Circadian rhythms in excretion**

Urinary pH, tubular secretion, renal blood flow, and glomerular filtration rate (GFR) all have an impact on renal excretion. During the day, the glomerular filtration rate (GFR) is at its highest, and at its lowest, is at night. Urine's pH changes from acidic to alkaline over the course of the day.[6,7]

2) Chronesthesy

It focuses on the examination of rhythmic variations in the target system's sensitivity and susceptibility to drugs.[6,7]

3) Chronotherapeutics

Chronotherapeutics is the study of how to time medication administration to match biological rhythms, or the rhythmicity of physiological, biochemical, and behavioural processes, in order to maximise medicinal efficacy and minimise side effects. The case for a novel pharmacologic approach to therapy is supported by evidence of circadian rhythms in medication kinetics, effects, and safety, as well as knowledge of day-night and other time-dependent predictions in symptom severity and risk of acute disease aggravation. It focuses on increasing the effectiveness and safety of pharmaceuticals by distributing their concentrations throughout the course of a day in accordance with the biological rhythms that determine illness.[8]

4) Chronergy

It addresses the rhythmic variation in pharmacological effects on the organism as a whole, including both favourable and undesirable effects.[9]

5) Chrono toxicology

It is a characteristic of chromodynamics and specifically refers to rhythm-dependent changes in the severity of side effects, patient sensitivity to medications, and symptoms.[9]

Concepts of chronopharmacology

The efficient absorption of a drug from the stomach or the injection site has always been the basis for drug distribution. The ideal zero-order drug delivery is the goal of second-generation drug delivery. Yet, the responses of living organisms to drugs are not "zero-order". They are essentially predictable resonating dynamic systems that need varied dosages of the drug given at predictable intervals during the circadian cycle through to achieve the desired and minimize undesirable pharmacological effects. Medical chronobiology is concerned in how periodic impacts on health and disease occur. Circadian rhythms have an effect on the majority of medical illnesses; chronopathology is the study of biological rhythms in disease processes and in gruesome and deadly incidents. Chronopharmacology is a branch of research that looks at how a medicine affects biological time.[10] When addressing day-related differences in therapeutic efficacy, concepts must be taken into account: circadian

changes in drug sensitivity and circadian changes in drug bioavailability (chronopharmacokinetics) (chronesthesia). The deliberate adjusting of a drug's dosage to match with rhythms in order to maximise therapeutic effectiveness and minimise negative effects is known as clinical chronopharmacology, sometimes known as chronotherapy. The liver is constantly exposed to relatively high amounts of ingested medications or poisons since it serves as the body's main line of defense for metabolic poisoning and is the target of several harmful chemicals. For pharmacological and toxicological investigations, it is essential to comprehend circadian impacts on transcriptional activities that regulate daily biochemical and a physiological process in the liver is a significant organ of metabolism and drug detoxification. It was discovered that the comparative activation levels of the enzymes in charge of the phase I and phase II categories of drug metabolism changed during the day.[11] Enzymes like cytochrome P450 oxidases generate reactive or polar groups for xenobiotics in phase I. Transferases, like glutathione S-transferases, combine the modified molecules to create polar compounds in phase II. As a result, when planning and analyzing toxicological research, it is crucial to take into account how the time of day impacts drug administration and animal sacrifice. Chronopharmacology studies both the pharmacological influences on bodily rhythms and the pharmacological influences on biological timing systems. A drug's pharmacokinetics (also known as chronopharmacokinetics) or pharmacodynamics (also known as signal transduction pathways or drug receptor expression) may be affected by temporal variations due to underlying changes in absorption, distribution, metabolism, and overall bioavailability (chronopharmacodynamics). A rhythmic neurotransmission system that incorporates temporal fluctuations in neurotransmitter levels, receptors, and second messengers can be used to describe chronopharmacodynamics as it relates to psychotropic medicines. Also, it is important to consider how toxicity and adverse side effects change over time (chronotoxicity).[10] The study of drug delivery systems that release a bioactive substance at a rate that, in theory, corresponds with the biological need for treating a certain condition is known as chronopharmacology. In order to maximise therapeutic response and minimise undesirable drug side effects, chronotherapy therefore encourages the use of temporal features of the patient and the illness process, such as the treatment of sleep and mental health concerns with light therapy or hormonal intervention.[12] It has been demonstrated that the aetiologies of many diseases exhibit well-established oscillatory cycles. Research on chronotherapy for asthma has been extensive.[13] At night, airway resistance steadily rises in asthmatics. Normal lung function fluctuates throughout the day and is lowest in the morning. This drop is particularly pronounced in asthmatics. As

chronotherapies for the management of asthma, theophylline, b2-adrenoceptor agonists, and oral corticosteroids have all been utilised.[13] All of them aim to lessen the overnight rise in airway resistance. The chronobiology, chronopharmacology, and chronotherapeutics of osteoarticular pain are also well covered.[14] Patients with osteoarthritis often have pain that is worse in the morning and progressively gets better over the day, in contrast to persons with rheumatoid arthritis.[13] A variety of drugs used to treat rheumatic conditions have various therapeutic and detrimental effects depending on the time of day that a treatment is taken. Chronotherapy should be timed so that the severe pain associated with all forms of arthritis occurs when the drug's blood levels are at their peak. If you have osteoarthritis, lunchtime to midafternoon is the best time to take a non-steroidal anti-inflammatory drug like ibuprofen. The same drug might be more useful for people with rheumatoid arthritis if used after meals. Many processes in the gastrointestinal tract exhibit circadian rhythms.[15] While gastric emptying and small bowel motility are all slower at night, gastric acid production is at its highest. These 24-hour rhythms have a considerable impact on the pharmacokinetics of orally administered drugs because drug breakdown, solubility, and absorption happen more slowly at night since stomach motility and emptying are slower. The reduction of nocturnal acid generation is essential for duodenal ulcer repair. Thus, the recommended dosage for H2-antagonists in people with active duodenal ulcers is once daily at bedtime. Circadian patterns can be observed in cardiac events. Studies have shown an increase in the frequency of myocardial infarction in the early morning, sudden cardiac death, stroke, and bouts of ischemia. This is due to the circadian rhythmicity of various cardiovascular system activities, including blood pressure, heart rate, stroke volume, cardiac output, and blood flow.[16] For instance, mornings see a rise in platelet aggregability and a decrease in fibrinolytic activity, which causes the blood to be somewhat more coagulable.[18] During the sleep cycle, blood pressure is at its lowest, and it quickly increases when you first wake up in the morning. Furthermore, diurnal variations in lipid fractions in both sick and healthy participants may be responsible.[17] Studies with b-hydroxy b-methylglutaryl-CoA reductase inhibitors (statins) showed that evening dosing was more efficient than morning administration. Hepatic cholesterol production occurs in a circadian cycle.[18] Diabetes has also been thoroughly researched for the circadian changes of glucose and insulin, and their therapeutic significance in the case of insulin replacement has been examined.[19] Devices like continuous subcutaneous insulin infusion (sensor-augmented insulin pumps) and real-time continuous glucose monitoring are particularly significant. According to studies on both humans and animals, cancer chemotherapy may be more beneficial and less harmful if it is provided at

periods that capitalize on tumour cell cycles while being less destructive to healthy tissue. The blood supply to tumours and the rate of tumour growth are both up to three times higher during the daily activity phase of the circadian cycle than they are when it is in its daily rest phase. The potential for improving current cancer treatment options and maximising the production of new anticancer or supportive compounds is further demonstrated by the chronotherapy method.[19] When treating brain tumours with gliobastoma treatment, chronotherapeutic drug sensitivity may be essential. Recent studies have shown that cellintrinsic circadian rhythms affect the cytotoxicity of DNA alkylating medicines like temozolomide in glioblastoma cells from mice and humans. A few hours before the rhythmic peak production of the mPER2 protein, curcumin was administered adjuvantly with chemotherapeutic drugs like cisplatin or doxorubicin in glioblastoma, and this resulted in cell death. There has long been information available on the chronopharmacology of many drugs with CNS effects. The effects of antipsychotic and antidepressant medicines have been the subject of numerous chronopharmacologic studies. Even when medications were studied using the same endpoints, the timing of treatment effectiveness along the circadian cycle varied. For instance, when the effects of dosing time on the pharmacological activity of different antidepressants acting on serotonergic, noradrenergic, and/or dopaminergic neurons were explored, all antidepressants reduced immobility, but their activities varied depending on the dose time. Furthermore, the peak time frequently changed depending on the parameter tested for a particular medicine.[20]

Chronopathology

Chronopathology focuses on the issue of timing disruption in critical biological processes. It discusses several occurrences that arise from the aberration of chronological sequences, together with their traits, root causes, importance in prognostic and diagnostic analysis, and therapeutic ramifications. Diseases appear at distinct times in particular creatures. The susceptibility to the frequency of diseases, the frequency of accidents, and the mortality rate are all influenced by annual and weekly cycles. The biological rhythm frequently deviates. For instance, blood pressure displays a variety of elements. In specific everyday circumstances, as well as when activity and rest cycles are in play, abnormalities might happen.[21] Chronopathology is the study of these shifting occurrences in connection to the function of the day-night cycle in diseases and functional disorders of organ functioning. Jet lag and shift workers are the two situations where this science is most frequently required.

Chronopathology makes it easier to pinpoint various stages of departure from the norm. Understanding time-dependent qualities can be crucial for correctly identifying and treating a disease. The cornerstone for medicines with a therapeutic time period is intelligent anatomy.

Chronophysiology

It is a branch of chronobiology that focuses on the chronological arrangement of physiological processes. The timing of natural biological processes is covered in the research. Chronophysiology discusses how biological systems and processes of organisms connect to one another in terms of time and deals with the phenomenon of morning folks and night owls.[22] The 24-hour rhythm is regulated by the human body. We have a biological clock inside of us called the circadian rhythm that helps us anticipate daily recurring occurrences and respond physiologically best to changing environmental conditions. We exist in a cycle of day and night. Our biological rhythm, which is ingrained in our DNA, is influenced by indicators like light, darkness, and temperature. Practically important bodily functions are governed by different rhythms. The amounts of hormones, neurotransmitters, ingested sugar molecules, and antibodies within blood cells change during the course of the day. A few modifications serve as crucial pacemakers for various organ responses. Even the development of sickness and the severity of its symptoms are driven by an internal clock. This is especially true for epileptic seizures, depression, and asthma. The circadian rhythm has a significant influence on overall health and wellness. For instance, time shift can have similar effects as jet lag in terms of difficulty sleeping, difficulty focusing, and even sadness. Shift workers who exhibit signs of persistent disruption may experience much more severe and long-lasting issues. We can only develop the energy required to maintain health when we modify our lifestyle to coincide with our internal cycles.[23]

Chronobiology

It is a branch of biology that focuses on timing events in living organisms, such as how they respond to the sun and moon's cycles or other periodic (cycle) events. The term "biological rhythms" refers to these cycles. The term "chronobiology" is a combination of the Greek letters o (chrónos, which means "time") and biology, which stands for the study or science of life. The related terms chronomics and chronome have occasionally been used to characterize the molecular processes underlying chronobiological events or their more quantitative characteristics, particularly when comparing the cyclicity of various animals. Chronobiological studies include, but are not limited to, comparative anatomy, physiology,

genetics, molecular biology, and behavior of organisms in connection to their biological cycles. Ecology, evolution, development, reproduction, and epigenetics are further considerations.[24]

History

The French researcher Jean-Jacques d'Ortous de Mairan first identified the movement of plant leaves as a circadian cycle in the 18th century. The Swedish botanist and scientist Carl Linnaeus (Carl von Linné) created a flower clock in 1751 utilizing particular flowering plant species. He created a clock by arranging the chosen species in a circle; the flowers that opened at each certain hour served as the hands of the clock. He cited the hawk's beard plant, whose blooms emerged about 6:30 am, and the hawkbit, whose flowers did not open until 7 am, as examples of plants in the daisy family.[25]

The discipline of chronobiology was founded at a meeting held at Cold Spring Harbor Laboratory in 1960. The phase response curve, which Patricia DeCoursey also invented in 1960, has since grown to be one of the most crucial tools in the field. The term "circadian" was created by University of Minnesota professor Franz Halberg, who is commonly referred as as the "founder of American chronobiology." Halberg was not chosen to lead the Society for Research in Biological Rhythms in the 1970s; Colin Pittendrigh was. Pittendrigh had a background in evolution and ecology, whereas Halberg opted to focus more on the human and medical elements. Under Pittendrigh's supervision, members of the Society carried out fundamental research on a range of organisms, including both plants and animals. Financing for this kind of research on any species save mice, rats, people, and fruit flies has proven difficult in recent years.[26]

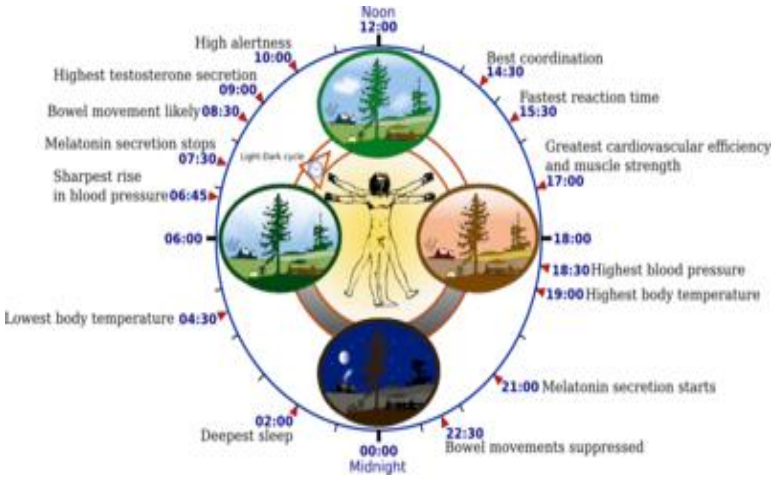

Figure 1: DOI:10.7897/2230-8407.04307.

Treatment of cancer through chronotherapy

Despite significant advancements in cancer treatment in the second half of the 20th century, it is still evident that patients experience unfavorable side effects and that cancer cells develop medication resistance. Because of this, chemotherapy does not always entirely cure all malignant illnesses; however, cure rates for choriocarcinoma, testicular cancer, and malignant lymphoma range from 50 to 90%. Chronotherapy has grown in favour as a method of resolving these problems during the past 20 years. Chronotherapy aims to coordinate the administration of medication with the circadian rhythms of chemotherapeutic adverse effects and cancer cell sensitivity. In 1959, Halberg and Stephens proposed the idea of "circadian rhythm." Since then, it has been discovered that the suprachiasmatic nucleus (SCN) is a representation of the biological clock, producing biological rhythms under the control of clock genes like PER1, PER2, and PER3, CLOCK, BMAL1, TIM, CRY1, CRY2, and tau, and coordinating peripheral oscillators for tasks like cell proliferation and cellular metabolism.[27] The SCN uses light/darkness changes to calibrate cycle length, both directly and indirectly through the pineal body's release of melatonin (Fig. 1). Circadian rhythms are created by period genes[28] and the proteins that these genes make. The CLOCK/BMAL1 complex, whose activity is blocked by the PER1/PER2/PER3/CRY1/CRY2/TIM complex, promotes PER transcription. A negative auto-feedback loop, which is how this enormous complex works, is essential for creating circadian oscillation. The circadian rhythm signals generated by this biological clock are received by the pineal body and the supra-cervical sympathetic nucleus. The regulation of biological processes, including the immune system, endocrine system, and autonomic nervous system, is a concern of created biological rhythms. These systems are all crucial for preserving homeostasis and preventing various diseases. The initial experimental trials in cancer chronotherapy were conducted by Halberg et al.[29] In the years that followed, Levi's team conducted a large number of experimental and clinical investigations in this area, concentrating in particular on the chronopharmacology and chronotherapeutics of 5-FU, both by itself and in conjunction with other anti-cancer medicines.[30] Moreover, Hrushesky's team investigated chronotherapy for advanced renal cell carcinoma and other gynaecological and genitourinary tumours. These trials proved that chronotherapy was superior to traditional chemotherapy in terms of response and adverse effects.[31]

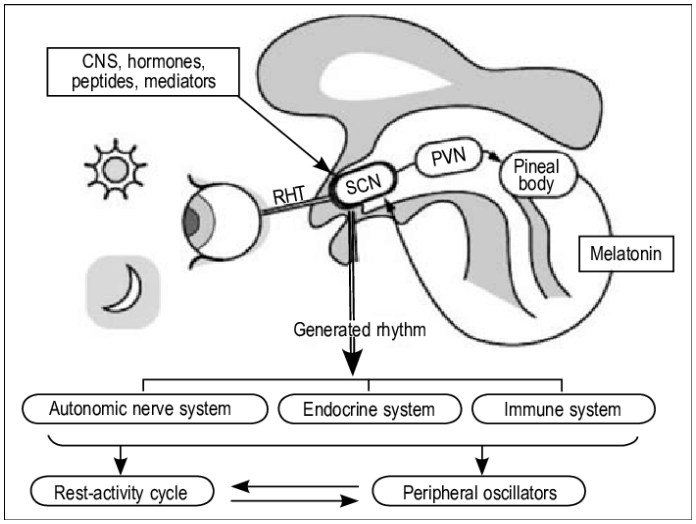

Fig. 1: Scheme of human circadian system. RHT, Retinohypothalamic tract; SCN, suprachiasmatic nucleus; PVN, paraventricular nucleus.

DISCUSSION

Combining surgical intervention with chemotherapy, radiation, and immunotherapy is crucial for the treatment of cancer. Chemotherapy and surgery, however, have been demonstrated to be ineffective for treating colon cancer patients who have liver metastases.[32] Indications for surgical treatment of liver metastases in colorectal cancer often include the following: More than 1 cm of surgical clearance at the time of resection, less than four liver metastatic lesions, no distant extrahepatic metastases, no metastases to the lymph nodes draining the liver, and no adversely placed metastatic lesions are all positives. These indications would not be applicable when patients respond favorably to chronotherapy with!-OHP + 5-FU + FA, making it possible to remove liver metastases to enhance prognosis.[33] According to the research of, we now believe that individuals with liver metastases who are receiving chronotherapy and surgery for their colon cancer may be cured. First off, chronomodulated administration has made it possible to provide anti-cancer drugs at full, effective doses due to a reduction in side effects. Second, recently created anti-cancer drugs like!-OHP, a platinum complex molecule with an entirely different mode of action from cisplatin, have been shown to be suitable for chronotherapy[34] Thus, clinical investigations to verify the effectiveness of!-OHP in accordance with chronotherapeutic principles and in combination with numerous anti-cancer drugs are currently being conducted. The suitability of chronomodulated delivery of novel anti-cancer medications, such as molecular targeting medications, also merits investigation. The European Organization for Research and Treatment of Cancer (EORTC) is now overseeing clinical trials using chronomodulation for numerous anti-cancer medicines in diverse malignant disorders[35] The chronomodulation technique is used in radiation[36] and

may be extended to immunotherapy, which is anticipated to be useful against autoimmune, infectious, and cancerous diseases. Chronotherapy will be acknowledged as a more efficient way to treat diseases other than cancer as molecular chronobiology develops and its mechanisms are better understood. The emergence of chronotherapy as a recognised therapeutic approach with the ability to go beyond the restrictions of existing treatments for cancer and other difficult diseases is likely something we will see throughout this first decade of the twenty-first century.[37,38]

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