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ORIGINAL ARTICLE

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Stress appraisal and emotion regulation mediate the association between mindfulness and affect in cancer patients: Differential mechanisms for positive and negative affect

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Abstract

Objective: Cancer patients are at an increased risk for affective problems, including feelings of anxiety and depression. Mindfulness has been linked to an array of benefits for affective functioning in various populations including cancer patients, but the mechanisms underlying this relationship are still poorly understood. Based on emotion-regulation and stress-coping models, this study examined the potential mediating role of stress appraisal and coping strategies in the associations between mindfulness and cancer patients' positive and negative affect.

Methods: For this cross-sectional study, 245 cancer patients completed self-report questionnaires measuring mindfulness (FFMQ), positive and negative affect (PANAS), stress appraisal (SPSI-R:S), coping through positive reappraisal and positive refocusing (CERQ), rumination (RRQ), and distraction (COPE). Serial mediation analyses were conducted using the regression-based bootstrapping method.

Results: Higher levels of mindfulness were associated with higher levels of positive affect; this relationship was mediated via stress appraisal and positive reappraisal. We also found an indirect effect from mindfulness directly via positive reappraisal to positive affect. In addition, higher levels of mindfulness were negatively associated with negative affect; this relationship was mediated via stress appraisal and rumination, with also an indirect effect from mindfulness directly via stress appraisal to negative affect.

Conclusions: Results suggest that stress appraisal and distinct coping strategies mediate the relationship between mindfulness and affect. Mindfulness may provide benefits for cancer patients' affect by allowing adaptive stress appraisal and ways of coping through more positive and less negative thinking.

KEYWORDS

affect, cancer, coping, mediation, mindfulness, oncology, positive reappraisal, positive refocusing, rumination, stress

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1 | BACKGROUND

Cancer is one of the most prevalent chronic and life-threatening diseases and a leading cause of death worldwide. For many individuals, receiving a diagnosis of cancer and its treatment are stressful and sometimes even traumatic experiences, with a significant group of people with cancer reporting affective problems.^{1,2} These problems can worsen patients' quality of life, and compliance to treatment and healthy lifestyle.³ Research on the prevalence of negative affect (NA), also referred to as distress, found that, on average, one of four cancer patients experiences feelings of emotional distress, including feelings of anxiety, fear, vulnerability, sadness, anger, irritability, guilt, and shame.^{1,2} It has also been found that cancer patients may experience a lack of *positive affect* (PA),⁴ which refers to feelings of joy, peace, happiness, enthusiasm, and contentment.⁵ These two types of affective states can co-occur in cancer patients over a certain period of time,⁴ as these affective states are generally weakly related to each other, as proposed by theory.⁵

These affective problems in cancer patients have urged researchers in the field of Psycho-Oncology to investigate factors that support patients' psychological adaptation to cancer. One factor that has received much attention in the past decade is mindfulness.^{6,7} Mindfulness has been described as "the awareness that emerges through paying attention on purpose, in the present moment, and nonjudgmentally to the unfolding of experience moment by moment".⁸ Two core components of mindfulness can be distinguished namely attention regulation, and an attitude of curiosity, openness, and acceptance.⁹ It has been found that people with cancer who are more mindful report less psychological distress, compared to those who are less mindful.¹⁰ Mindfulness may allow patients a heightened awareness of their body, including discomfort and distress, and respond to these experiences in a nonjudgmental manner, subsequently stimulating the restoration of the body, rest for the mind, and a sense of inner peace. Results from systematic reviews and meta-analyses showed that mindfulness-based interventions are effective in managing and reducing negative affect and bolstering positive affect and positivity in cancer patients,^{6,11} which is in line with the broader evidence for the efficacy and benefits of mindfulness-based interventions in healthy people and people with another somatic or mental illness.^{12,13}

Knowing that mindfulness cultivation may be beneficial for cancer patients' affect, an important next step now is to better understand why or how is mindfulness related to less negative affect and more positive affect. Various models have been proposed to define mindfulness and its potential impact on affect.⁹ These mechanisms, which are likely interconnected, involve attention regulation, body awareness, emotion awareness and regulation, and shifts in self-perspective.^{9,14} In the context of difficult life circumstances, mindfulness may be particularly useful for a greater awareness and attention regulation, as means to regulate emotions and cope with stressful experiences.

The most relevant and commonly used model of stress-coping is by Lazarus and Folkman (1984), who define coping as "constantly changing cognitive and behavioral efforts to manage specific external and/or internal demands that are appraised as taxing or exceeding the resources of the person".¹⁵ According to the model, we appraise an event we encounter as positive, negative (e.g., threatening), or neutral and our abilities to cope with the event (i.e., *primary and secondary stress appraisal*), followed by cognitive and behavioral efforts to reduce the problem and difficult emotions (i.e., *coping*).¹⁵ Coping has been categorized into two dimensions: *adaptive* (e.g., coping aiming at dealing with the difficulty and/or the associated emotions, such as positive reframing) and *maladaptive* (e.g., coping to avoid, deny, or escape the stressor or associated emotions, such as disengagement, distraction and rumination).¹⁶

Mindfulness is assumed to reduce habitual reactive and maladaptive appraisal and coping responses, hereby providing the individual a greater attention capacity and broader perspective on experiences. Therefore, more mindful individuals may employ more adaptive coping strategies and less maladaptive coping strategies.^{9,17,18} There is evidence that especially rumination is an important mechanism that may explain the relationship between mindfulness and affect.^{12,19} A related and relevant theory in the context of mechanisms underlying mindfulness that focuses specifically on PA is the Mindfulness-to-Meaning Theory (MMT).²⁰ The theory suggests that mindfulness allows one to decenter from the experience of stress, to broaden one's attention, and reappraise adverse circumstances, hereby not only reducing distress but also promoting positive affect.²⁰ Mindfulness may inhibit a cycle of negative emotional reactions and promote a shift toward positive aspects of the situation.²⁰ Higher levels of mindfulness have been associated with greater use of positive refocusing (i.e., turning attention to the pleasant aspect of an experience) and positive reappraisal (i.e., reassigning positive meaning of a stressful event).^{21,22} Only few studies in cancer patients investigated the role of stress appraisal and coping as mediators in the association of mindfulness with affect. For example, a cross-sectional study in colorectal cancer patients found that mindfulness was related to lower threat appraisal of cancer, subsequently related to less depressive symptoms.²³

To the best of our knowledge, this is the first study in cancer patients that aims to examine the role of both stress appraisal and several adaptive and maladaptive coping strategies as mechanisms in the relationship between mindfulness and affect. As differential relationships have been found between mindfulness and positive and negative affect,²⁴ separate analyses were conducted for positive and negative affect. This study focused on adaptive coping strategies such as positive reappraisal and positive refocusing, as well as maladaptive coping strategies like rumination and seeking distraction, based on existing empirical evidence.

2 | METHODS

2.1 | Participants and procedure

This cross-sectional study used data from a study on mindfulness and self-compassion in cancer patients.²⁵ The data collection was approved by the ethical review board of the University Medical Center Groningen (UMCG), the Netherlands. Cancer patients were

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recruited through the radiation oncology department from April 2011 to November 2011. Patients were included if they were 18 years old or older, received a cancer diagnosis maximally five years ago, were treated with a curative intent, and completed radiotherapy treatment for at least two months. They were excluded if they lacked proficiency in Dutch or were diagnosed with a severe psychiatric disorder. Breast cancer patients had to be excluded, as they were participating in other research and, therefore, could not be approached for the current study. In total, 245 cancer patients met eligibility criteria, gave their informed consent, and were included in the study.

2.2 | Measures

2.2.1 | Mindfulness

Mindfulness was assessed with the 39-item Five Facets Mindfulness Questionnaire (FFMQ).²⁶ The FFMQ measures five facets of mindfulness: observe, describe, act with awareness, non-judge, and nonreact. Participants were asked to rate the extent to which the items (e.g., "I watch my feelings without getting lost in them.") were true for them on a five-point Likert scale ranging from 1 (never or very rarely true) to 5 (very often or always true). The sum score can range from 39 to 195 with higher scores indicating higher levels of mindfulness. In this study, the FFMQ showed good internal consistency ($\alpha = 0.82$).

2.2.2 | Positive and negative affect

Affect was measured using the 20-item Positive and Negative Affect Schedule (PANAS)⁵ which contains two 10-item subscales that assess PA and NA. Participants were asked to rate the degree to which each descriptor (e.g., enthusiastic, alert, nervous, and distressed) applied to them in the past week on a five-point Likert scale ranging from 1 (very slightly or not at all) to 5 (very much). Sum scores for both subscales can range from 10 to 50, with higher scores indicating higher levels of positive or NA respectively. In this study, the internal consistency of the PANAS was good for PA ($\alpha = 0.89$) and NA ($\alpha = 0.88$).

2.2.3 | Stress appraisal

Stress appraisal was assessed using the 5-item negative problemsolving orientation subscale of the Social Problem-Solving Inventory—Revised: Short Form (SPSI-R:S).²⁷ Participants were asked to indicate how true each statement is for them, regarding how they deal with everyday life problems (e.g., I feel threatened and anxious when I have to solve and important problem, I doubt if I can solve a difficult problem no matter how hard I try), on a five-point Likert scale ranging from 0 (not at all true) to 4 (extremely true). The sum score may range from 0 to 20, with higher scores indicating a more negative problem-solving orientation, indicating a higher stress appraisal. In this study, the subscale showed good internal consistency ($\alpha = 0.86$).

2.2.4 | Positive reappraisal and positive refocusing

These coping strategies were measured by the 4-item subscale "positive reappraisal" and 4-time subscale "positive refocusing" of the Cognitive Emotion Regulation Questionnaire (CERQ).²⁸ Participants were asked to indicate how often they think in a certain way (for positive reappraisal: e.g., "I think I can learn something from the situation"; for positive refocusing: e.g., "I think of something nice instead of what has happened") when managing stressful life events on a five-point Likert scale ranging from 1 (almost never) to 5 (almost always). For each subscale, scores can range from 4 to 20, with higher scores indicating greater use of positive reappraisal and positive refocusing, respectively. The internal consistency was good (positive reappraisal, $\alpha = 0.83$; positive refocusing, $\alpha = 0.87$).

2.2.5 | Rumination

Rumination was measured with a 12-item rumination subscale of the Rumination-Reflection Questionnaire (RRQ).²⁹ Participants were asked to indicate the extent to which they engaged in ruminative thinking (e.g., "I often find myself reevaluating something I have done") on a five-point Likert scale ranging from 1 (strongly disagree) to 5 (strongly agree). The sum score may range from 12 to 60, with higher scores indicating more rumination. In this study, the internal consistency was good ($\alpha = 0.88$).

2.2.6 | Distraction

Distraction was assessed with a 4-item subscale of the COPE.³⁰ Participants were asked to indicate how frequently they used distraction as a coping strategy (e.g., "I have been doing something to think about it less, such as going to movies, watching TV, reading, daydreaming, sleeping, or shopping") on a four-point scale ranging from 1 (usually do not do this at all) to 4 (usually do this a lot). The sum score may range from 1 to 16 with a higher score indicating higher perceived use of distraction. The internal consistency was poor in this study ($\alpha = 0.54$) even after dropping item(s). Therefore, the distraction subscale was excluded from analyses.

2.3 | Statistical analysis

Statistical analyses were conducted using IBM SPSS Statistics 28.0. Descriptive statistics were performed on demographic and cancerrelated variables to characterize the study population. Furthermore, descriptive statistics, reliability analysis, and Pearson's correlations among all study variables were also performed. The total, direct, and indirect effects were estimated using serial multivariable mediation model (model 6) of the PROCESS macro v4.0 for SPSS³¹ which calculated 95% bootstrap confidence intervals for parameter estimates (with $N \sim 0$ 5000 bootstrap resamples). The predictor variable (X_i) was mindfulness. Mediators (M_i) were stress appraisal, positive reappraisal, positive refocusing, and rumination. The outcome variables (Y_i) were PA and NA. A total effect (c) refers to the relationship between mindfulness (X_i) and affect (Y_i) without controlling for stress appraisal and coping (M_i). A direct effect refers to the relationship between mindfulness (X_i) and affect (Y_i) after controlling for stress appraisal and coping (M_i) . The indirect effects were the effects of mindfulness (X_i) on affect (Y_i) through stress and coping (M_i) .

Two models were used to examine the relationships between mindfulness, stress appraisal, coping, and affect. Model 1 included PA as the outcome variable, while model 2 included NA as the outcome variable. Age and type of cancer were the only significant demographic and clinical factors related to affect, serving as covariates in both models. Furthermore, the analysis utilized the PROCESS macro, which employed list-wise deletion, resulting in a sample size of 232 for Model 1 (PA) and 233 for Model 2 (NA) after excluding cases with missing values.

RESULTS 3

3.1 | Sample characteristics

Patients' characteristics are presented in Table 1. The sample consisted predominantly of male cancer patients (75.1%), and the most common cancer type was urological cancer (53.1%).

3.2 **Bivariate analysis**

Descriptive statistics and correlations for study outcomes are presented in Table 2. First, mindfulness was significantly related to both PA (0.51**) and NA (-0.40**). Second, mindfulness was significantly negatively correlated with stress appraisal (-0.40**), positively related to positive reappraisal (0.42**), and negatively related to rumination (-0.33**), with only a weak relationship with positive refocusing (0.15*). PA and NA related differently to stress appraisal and coping.

3.3 Serial mediation analyses

3.3.1 Model 1: Mindfulness and positive affect

Figure 1 depicts the mediational model for PA. Mindfulness was significantly associated with less stress appraisal ($a_1 = -0.38$,

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TABLE 1	Demographic and clinical characteristics of the study
sample.	

Demographic variables

	N	245
	Age (mean, SD)	65.35 (12.01)
	Gender (N, %)	
	Male	184 (75.1)
	Education level (N, %)	
	Low	77 (31.4)
	Middle	89 (36.3)
	High	79 (32.2)
CI	inical variables	
	Years since diagnosis (mean, SD)	2.39 (1.39)
	Cancer type (N, %)	
	Urological	130 (53.1)
	Lung	20 (8.2)
	Hematological	17 (6.9)
	Gynecological	21 (8.6)
	Other	27 (11.0)
	Mixed	30 (12.2)
	Received treatment (N, %)	
	RT	59 (24.0)
	RT + surgery	73 (30.8)
	RT + chemo	24 (9.8)
	RT + surgery + chemo	33 (13.5)
	RT + hormone	20 (8.2)
	RT + surgery + hormone	16 (6.5)
	Other	20 (8.2)
	Recurrence (N, %)	
	Yes	38 (15.5)

Abbreviation: RT, Radiotherapy.

p < 0.01) and more positive reappraisal ($a_2 = 0.49$, p < 0.01), but not with positive refocusing or rumination. Stress appraisal was significantly associated with more positive reappraisal ($d_1 = 0.20, p < 0.01$) and more rumination ($d_3 = 0.44$, p < 0.01). Positive reappraisal and positive refocusing also had a direct effect on PA ($b_2 = 0.22$, p < 0.01and $b_3 = 0.14$, p < 0.01 respectively).

The indirect effects of mindfulness on PA through stress appraisal and then positive reappraisal were significant $(a_1d_1b_2 = -0.02, SE = 0.01, 95\% CI [-0.037, -0.003])$. The indirect effect of mindfulness on PA through only positive reappraisal was also significant ($a_2b_2 = 0.11$, SE = 0.04, 95% CI [0.034, 0.195]). There were no other significant indirect effects. After controlling for stress appraisal and coping, mindfulness still had a significant direct effect on PA (c' = 0.39, p < 0.01) and a significant total effect on PA

	Descriptive statistics		Pearson's correlation coefficients, r						
Study variables	Mean (N = 245)	SD	1	2	3	4	5	6	7
1. FFMQ, mindfulness sum score	134.38	15.38	-						
2. PANAS, positive affect	29.42	7.46	0.51**	-					
3. PANAS, negative affect	15.47	5.75	-0.40**	-0.10	-				
4. SPSI-R:S - NPO, stress appraisal	10.02	3.40	-0.40**	-0.10	0.46**	-			
5. CERQ, positive reappraisal	10.95	3.91	0.42**	0.47**	-0.07	0.03	-		
6. CERQ, positive refocusing	9.83	4.01	0.15*	0.32**	0.00	0.04	0.57**	-	
7. RRQ, rumination	32.35	8.14	-0.33**	-0.16*	0.48**	0.50**	-0.05	0.05	-

Abbreviations: CERQ, Cognitive Emotion Regulation Questionnaire; COPE, COPE inventory; FFMQ, Five Facets Mindfulness Questionnaire; PANAS, Positive and Negative Affect Schedule; RRQ, Rumination-Reflection Questionnaire; SPSI-R:S - NPO, Social Problem-Solving Inventory – Revised: Short Form - Negative Problem-Solving Orientation.

p < 0.05 p < 0.01



FIGURE 1 Parameter estimates for serial mediation model 1 with mindfulness as X and positive affect as Y (*p < 0.05, **p < 0.01). Path values represent completely standardized coefficients.

(c = 0.50, p < 0.01), when the mediators were uncontrolled. Hence, results revealed that mindfulness was indirectly related to PA through stress appraisal and positive reappraisal, and through positive reappraisal alone.

3.3.2 | Model 2: Mindfulness and negative affect

Figure 2 displays the mediation model for NA. Mindfulness was significantly associated with stress appraisal ($a_1 = -0.40$, p < 0.01) and positive reappraisal ($a_2 = 0.50$, p < 0.01), but not with positive refocusing or rumination. Stress appraisal was significantly associated with positive reappraisal ($d_1 = 0.21$, p < 0.01) and rumination ($d_3 = 0.45$, p < 0.01). Stress appraisal and rumination also had a direct

effect on NA ($b_1 = 0.19$, p < 0.01 and $b_4 = 0.30$, p < 0.01 respectively).

The indirect effects of mindfulness on NA through stress appraisal and then rumination were significant $(a_1d_3b_4 = -0.05, SE = 0.02, 95\%$ CI [-0.087, -0.027]). The indirect effect of mindfulness on NA through only stress appraisal was also significant $(a_1b_1 = -0.08, SE = 0.03, 95\%$ CI [-0.134, -0.024]). There were no significant other indirect effects. After controlling for stress appraisal and coping, mindfulness had a significant direct effect on NA (c' = -0.23, p < 0.01) and a significant total effect on NA (c = -0.39, p < 0.01) when the mediators were uncontrolled. Hence, results revealed that mindfulness was indirectly related to NA through stress appraisal and rumination, and through stress appraisal alone.



FIGURE 2 Parameter estimates for serial mediation model 2 with mindfulness as X and negative affect as Y (*p < 0.05, **p < 0.01). Path values represent completely standardized coefficients.

4 | DISCUSSION

This cross-sectional study in cancer patients aimed to reach a better understanding of how mindfulness is associated with affect. Results indicated that the relationship between higher levels of mindfulness and positive affect was mediated by use of positive reappraisal and via a combination of stress appraisal and positive reappraisal. The relationship between higher levels of mindfulness and lower levels of negative affect was mediated by stress appraisal and via stress appraisal in combination with rumination. Although preliminary, given the cross-sectional design, results suggest that stress appraisal and coping may explain the benefits of mindfulness for cancer patients' affect, with the specific mechanisms depending on the type of affect (i.e., negative or positive).

For positive affect, we found two significant indirect effect paths that could explain the association of mindfulness with affect. First, results suggest that cancer patients who reported to be more mindful experienced more positive affect as mindfulness helped them to positively reappraise stressful events. This result is in line with the Mindfulness-to-Meaning Theory, describing that mindfulness enables decentering from stressful experiences, reduces attentional bias to threat by broadening one's attention to embrace positive aspects of life, and promotes reappraisal of adverse circumstances, thereby not only reducing distress, but also fostering positive affect.^{20,21,32} The theory also proposes that metacognitive awareness arising from decentering may impede habitual and rigid stress responses and bolster use of active coping such as positive reappraisal.³² Our findings are congruent with a previous study in cancer patients, showing that more mindful cancer patients were more likely to pay attention to positive experiences and information and to use positive reappraisal to cope with adversity.²⁰

Results also suggest a more complex mediation for positive affect which involves stress appraisal. Results show that more mindful cancer patients were less likely to perceive problems as threat and feel more personal control and confident about their abilities to manage problems, and that they make more use of positive reappraisal. This reasoning is in line with research on mindfulness from a self-determination perspective,³³ with mindfulness being beneficial for our well-being, by strengthening autonomy, a concept closely related to personal control. From a self-determination perspective, mindfulness is assumed to facilitate the fulfillment of basic needs, including autonomy, by increasing awareness that one has a choice in how to respond to stressful situations and to act autonomously.³⁴ Such a sense of autonomy and control have been found to be important for the experience of positive affect.³⁵ As previous studies in cancer patients focused on the role of threat appraisal in the relationship between mindfulness and negative affect, our results add to literature, as they point out that stress appraisal also play a role in the relationship between mindfulness and positive affect.

It should be noted that we did not find significant indirect effects of mindfulness with coping by means of positive refocusing or rumination, as others have found. A possible explanation for these different results could be differences in the assessments of the constructs. Whereas Garland et al.²⁰ asked participants about the extent to which they attend, think about, and focus on positive information to measure positive refocusing,²⁰ we asked patients to what extent they use positive thinking *instead* of thinking about what has happened. Therefore, our measure does not merely assess positive attention. Furthermore, in mindfulness research on mechanisms, rumination has generally been more strongly associated with negative outcomes such as forms of negative affect as depression and anxiety rather than positive forms of affect.^{12,13,19}

For negative affect, we also found two significant mediation paths. First, less mindful cancer patients reported greater perceived threat and less sense of control and confident about one's abilities to manage problems, and consequently a greater experience of negative affect. Based on the aforementioned self-determination theory,^{33,36} mindfulness may reduce negative affect by increasing awareness that one WILEY-

has a choice in how to respond to stressful situations and to act autonomously and adaptively.³⁴ Second, we also found a more complex mediation which involves rumination. Results suggest that less mindful cancer patients reported more negative affect, through greater stress appraisal and more use of rumination. This results is in line with previous studies showing that more mindful cancer patients may experience less negative affect, as they are less likely to perceive events as stressful and threatening (i.e., lower stress appraisal)²³ and are less likely to ruminate.³⁷ Additionally, Mindfulness-to-Meaning Theory suggests that the decentering aspect of mindfulness hinders perseverative cognition, such as rumination, by facilitating the release or "letting go" of negative thoughts and emotions, which in turns, alleviates psychological distress.³² All together, these results add to the evidence that mindful individuals exhibit a greater capacity to accept experiences as a natural part of life and to disengage from brooding and dwelling on negative feelings (i.e., rumination). We did not find significant indirect effects of adaptive coping strategies in the negative affect model, which is in line with previous research that negative affect is often associated with maladaptive coping but not adaptive coping.³⁸

4.1 | Study limitations

The study was strongly conceptually and theory-driven, included a range of stress appraisal and coping strategies, and distinguished positive and negative affect, as these affective states may differ in their association with mindfulness and underlying mediators,^{24,39} Yet several limitations also need to be considered when interpreting our results. First, due to the cross-sectional design, we could not test the temporal order or make causal inferences. Previous intensive longitudinal research did provide evidence that mindfulness and rumination *precede* affect, rather than the other way around.⁴⁰ Second, although our results are in line with previous research in the general population and other patient samples, the specific characteristics of our patient sample may limit the generalizability of results to other cancer patients and populations. Third, the questionnaire we used to assess stress appraisal does not distinguish primary and secondary stress appraisal. Thus, our findings may not fully represent the stress-coping model.

4.2 | Clinical implications

Our results provide insights into why mindfulness may be beneficial for people with cancer. Mindfulness may reduce the perception of cancer-related events as threatening while bolster a sense of confidence and control in one's capacities to deal with difficult stressful events. In addition, mindfulness may help people to disengage from ruminative thinking about themselves and negative events, and to find (positive) meaning in managing the cancer diagnosis and treatment, such as an increased appreciation of their relationships with loved ones and "small" things in life and greater awareness of priorities and personal values (so-called, *post-traumatic growth*). Given these benefits, it can be valuable to offer mindfulness-based

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interventions to cancer patients in clinical care, who are lacking mindfulness skills and are at an increased risk for affective problems.

5 | CONCLUSIONS

Our results suggest that distinct mechanisms can explain the associations of mindfulness with cancer patients' positive and negative affect. Our findings also support the utility of stress-coping model in mindfulness research among cancer patients as distinct serial mediation processes through stress appraisal and coping were found for each outcome. All in all, this study provides insight into the complexity of how mindfulness may influence affect and are a step toward a better understanding of mindfulness and its benefits for our health and well-being.

AUTHOR CONTRIBUTIONS

Puttichai Tungtong developed the theoretical framework, performed analysis, and wrote manuscript. Adelita V. Ranchor supervised the project. Maya J. Schroevers supervised, verified methods, and contributed to interpretation of the results. All authors provided critical feedback and shaped the research and manuscript.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

Data of this study is available from the corresponding author upon reasonable request.

ETHICS STATEMENT

All procedures performed in studies involving human participants were in accordance with the ethical standards of the Ethical Committee at the University Medical Center Groningen. Informed consent was obtained from all study participants.

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